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WH

Protein-Energy Requirements under Conditions Prevailing in Developing Countries: Current Knowledge and Research Needs

THE UNITED NATIONS UNIVERSITY

From the CHARTER OF THE UNITED NATIONS UNIVERSITY

ARTICLE I

Purposes and structure

1. The United Nations University shall be an international community of scholars, engaged in research, post-graduate training and dissemination of knowledge in furtherance of the purposes and principles of the Charter of the United Nations. In achieving its stated objectives, it shall function under the joint sponsorship of the United Nations and the United Nations Educational, Scientific and Cultural Organization (hereinafter referred to as UNESCO), through a central programming and co-ordinating body and a network of research and post-graduate training centres and programmes located in the developed and developing countries.

2. The University shall devote its work to research into the pressing global problems of human survival, development and welfare that are the concern of the United Nations and its agencies, with due attention to the social sciences and the humanities as well as natural sciences, pure and applied.

3. The research programmes of the institutions of the University shall include, among other subjects, coexistence between peoples having different cultures, languages and social systems; peaceful relations between States and the maintenance of peace and security; human rights; economic and social change and development; the environment and the proper use of resources; basic scientific research and the application of the results of science and technology in the interests of development; and universal human value related to the improvement of the quality of life.

4. The University shall disseminate the knowledge gained in its activities to the United Nations and its agencies, to scholars and to the public, in order to increase dynamic interaction in the world-wide community of learning and research.

5. The University and all those who work in it shall act in accordance with the spirit of the provisions of the Charter of the United Nations and the Constitution of UNESCO and with the fundamental principles of contemporary international law.

6. The University shall have as a central objective of its research and training centres and programmes the continuing growth of vigorous academic and scientific communities everywhere and particularly in the developing countries, devoted to their vital needs in the fields of learning and resrarch within the framework of the aims assigned to those centres and programmes in the present Charter. It shall endeavour to alleviate the intellectual isolation of persons in such communities in the developing countries which might otherwise become a reason for their moving to developed countries.

7. In its post-graduate training the University shall assist scholars, especially young scholars, to participate in research in order to increase their capability to contribute to the extension, application and diffusion of knowledge. The University may also undertake the training of persons who will serve in international or national technical assistance programmes, particularly in regard to an interdisciplinary approach to the problems with which they will be called upon to deal.

ARTICLE II

Academic freedom and autonomy

1. The University shall enjoy autonomy within the framework of the United Nations. It shall also enjoy the academic freedom required for the achievement of its objectives, with particular reference to the choice of subjects and methods of research and training, the selection of persons and institutions to share in its tasks, and freedom of expression. The University shall decide freely on the use of the financial resources allocated for the execution of its functions. . . .

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PROTEIN-ENERGY REQUIREMENTS UNDER CONDITIONS PREVAILING IN DEVELOPING COUNTRIES: CURRENT KNOWLEDGE AND RESEARCH NEEDS

THE UNITED NATIONS UNIVERSITY

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FOREWORD

When the first expert group convened by the United Nations University (UNU) met in Tokyo in October of 1975 to determine priority areas within its World Hunger Programme, it selected, as one of four, the issue of "Human Nutritional Requirements Under Conditions Prevailing in Developing Countries and the Capacity of Local Diets to Meet These Needs." The others were "Post-Harvest Food Conservation," "Nutrition and Food Objectives in National Development Planning," and "Agricultural Production, Food, and Nutrition Interfaces."

The group considered that added information and understanding in these four areas could make a significant contribution to solving problems of world hunger and malnutrition, and that existing programmes were not adequately addressing them either nationally or internationally. The mechanisms available to the UNU which enable it to contribute to the solution of such pressing global problems are the instruments of scholarship, research, advanced training, and the dissemination of knowledge.

It was generally agreed that deficiencies of protein, energy, vitamin A, and iron were those of most serious concern to developing countries. In view, therefore, of the progress being made through WHO, FAO, bilateral, and private-agency efforts to study the occurrence and prevention of vitamin-A and iron deficiency, the UNU should, in co-operation with FAO and WHO, attempt to accelerate current studies of the protein and energy needs of individuals and population groups in developing countries.

Following this decision, the first step was to convene a working group, and it met in San José, Costa Rica, 1–3 February 1977, to discuss the issues, summarize existing knowledge, and make research suggestions. The participants were: Dr. R. G. Whitehead, who served as Chairman, and Drs. Ann Ashworth, W. R. Beisel, J. D. L. Hansen, Po-Chao Huang, L. Mata, D. Picou, A. Pradilla, N. S. Scrimshaw, and V. R. Young. Valuable and frequently detailed comments on their report have since been received from Drs. G.

Arroyave, G. Beaton, M. Béhar, S. Berger, R. Bressani, S. J. Closa, D. Calloway, C. Garza, M. Hegsted, C. Meredith, B. Nicol, B. Nichols, P. Payne, R. Schneider, J. Waterlow, B. Torun, and F. Viteri. In addition, new data have been received from UNU-sponsored research by L. Fajardo, Cali, Colombia; J. S. Ju, Seoul, Korea; B. Torun, Guatemala City; H. Bourges, Mexico City; and A. Ashworth, Kingston, Jamaica. Additional relevant data have become available from research at INCAP, Guatemala; MIT, Cambridge, Massachusetts; Dunn Nutritional Laboratory in Cambridge, England; University of Buenos Aires, Argentina; and others. Taking all of these efforts into consideration, the Advisory Committee of the UNU World Hunger Programme at its second meeting in Guatemala in October 1977, proposed that a small drafting group attempt to blend these various reports into a single document that would not only serve to guide the development of the research programme sponsored by the University for this priority, but also be of wider value in encouraging research on the major issues involved.

The group chose Dr. Fernando Viteri, Chief of the Division of Biology and Human Nutrition, INCAP, Guatemala City; Dr. Roger Whitehead, Director of the Dunn Nutrition Unit, Cambridge, England; and Dr. Vernon Young, Professor of Nutritional Biochemistry, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts, to undertake the difficult task of taking into consideration differing points of view and interpretation, and integrating them into this report.

The purpose of the report is to indicate the current state of knowledge regarding protein and energy requirements and appropriate dietary allowances for various populations living under the conditions prevailing in developing countries and consuming local diets. Its principal function is to provide suggestions for needed research. FAO, WHO, and the UNU have agreed to co-operate closely in this programme area, and the report should be useful for all three. Some of the required research can be directly sponsored by the United Nations University, but the effort needed goes far beyond the resources of any single organization, and support from many sources will be necessary if satisfactory progress is to be achieved.

If the research recommended in this report is done, it should be possible in the future to know what the appropriate estimates are for protein and energy requirements and allowances for all populations, including those living under the conditions prevailing in developing countries and consuming diets quite different in physical characteristics and nuturient sources from those for which current data are most readily available.

Nevin S. Scrimshaw
Senior Adviser, World Hunger Programme

I. INTRODUCTION

Current estimates of protein and energy needs for normal, healthy individuals make no distinctions among population groups of differing ethnic backgrounds and environments because there are, at present, insufficient data to determine whether or not such distinctions are warranted. Similarly, no quantitative guidelines are available to allow for the various degrees of stress affecting all populations, especially the lower socio-economic groups within developing countries.

One of the major factors complicating the estimation of nutrient needs under the environmental conditions prevailing in many developing countries is the presence of widespread and repeated infection, both acute and chronic. Requirements for dietary energy and nutrients, especially protein, during and after infection have been of concern to nutritionists for many years.

The nutrition levels discussed in earlier reports of Joint FAO/WHO Expert Committees are intended to apply to healthy individuals. In this report, specific emphasis is given to considerations of the protein and energy requirements of, and allowances for, individuals and population groups in areas where acute and chronic infections are endemic, and where the patterns of living differ substantially from those in the industrialized countries, where the subjects lived from whom most of the available data concerning protein and energy requirements have been derived. The concern here is to identify the diets that will permit satisfactory recovery from both the infections that are a part of the existence of underprivileged populations and the mild to moderate malnutrition associated with them. This report does not deal with requirements for therapeutic diets for seriously ill individuals.

Dietary protein and energy are closely interrelated. Moreover, the issue of individual requirements is complicated by variations in the same person, depending on his daily circumstances, and the determination of safe allow-

ances for maintenance of the health of populations is even more confounded by this factor. This topic has been considered by numerous national and international committees, but, with the partial exception of information about infants and healthy young adults, there are few firm scientific data.

Most people in the world do not, and perhaps never will, receive the protein-rich foods characteristic of diets in Europe and North America. What are the implications for health of diets that differ so greatly in both sources of protein and energy and in the patterns in which they are consumed?

The critical questions are as follows.

(a) What are the relative requirements for dietary protein and energy under the various conditions prevailing for the populations concerned?
(b) Is there enough information to establish safe, practical allowances that are appropriate to the health needs of underprivileged populations?
(c) How valid are extrapolations of protein and energy needs, as determined in healthy subjects with constant and often highly refined diets, to diets of differing physical characteristics, foods, nutrient densities, bulk, and meal frequencies?
(d) Is it necessary to have different allowances for some populations, or are those currently established for normal, healthy populations adequate for all?

II. PROTEIN AND ENERGY REQUIREMENTS FOR BODY MAINTENANCE AND HEALTHY ORGAN FUNCTION

Energy

Estimates of successive FAO and joint FAO/WHO committees concerned with dietary energy allowances for healthy, well-nourished populations have been useful guidelines. It is recognized, however, that there is a great need for development and improvement of methods for determining the energy requirements of individuals, and for determining the energy needs and energy expenditure of different socio-economic and ethnic groups.

TABLE 2.1. Average energy availability in different countries relative to safe levels

Country	Mean *per capita* energy supply as % of requirement
Afghanistan	80
Bangladesh	88
Bolivia	76
El Salvador	80
Haiti	87
India	92
Indonesia	91
Liberia	88
Somalia	77
Tanzania	73
Mean developing world	93
Mean industrialized world	117

(Source: FAO: for projected deficits and surpluses, the International Food Policy Research Institute, cited in United Nations World Food Council, "Increasing Food Production in the Developing Countries," WFC/20, 14 April 1976.)

An examination of data on energy intake from different developing countries suggests that large proportions of the population are surviving and working on diets with energy contents well below these estimated average requirements, even when adjusted for lower body weight. (Examples are given in Table 2.1.) Raising dietary energy intakes to meet the allowances suggested in the 1973 FAO/WHO report (Ref. 1) has important economic and agricultural implications, and this underscores the need for adequate data on human energy requirements in order to develop effective governmental policies and to make the most efficient use of potential national resources.

Because individuals cannot indefinitely consume less than their physiological needs, adaptation to low calorie intakes must occur within the low-income populations of developing countries. The issue is the nature of the adaptation and its social and health costs. An alternative interpretation of the data is that current standards for energy intake may be too high for some of the populations to which they are applied, e.g., those in industrialized countries where physical activity is relatively low and in the more privileged population sectors of developing countries.

1. Adaptation to Low Energy Intakes

A primary adaptive mechanism appears to be a decrease in physical activity, which, for the adult, may mean limited activity apart from essential work to earn a living (Ref. 2). There is growing evidence that, in developing countries, low energy intake frequently limits the amount of daily work that can be performed, and that increased food results in greater productivity if work is available (Ref. 2). There is also an increase in the non-work activities essential to the development of human societies. Other mechanisms may contribute to increase the efficiency with which dietary energy is used to meet the body's needs when energy intakes are less than the levels to which individuals in North America and Europe are accustomed (Ref. 3). Similarly, there is evidence that an adaptation occurs in response to excess energy intakes (Ref. 4), but the precise nature of the metabolic changes that are responsible for the adaptations, and the extent to which they minimize changes in bodily composition and prevent deterioration in health, are poorly understood.

For the pregnant woman, the birth weight of the child will be reduced when calories are in short supply during gestation, and there will be a resulting increase in neonatal and perinatal mortality (Refs. 5, 6), and, according to INCAP studies, not only is there increased morbidity, mortality, and growth retardation in the first year of life but also reduced performance on tests of learning and behaviour in later, pre-school years (Ref. 7).

For children, either a low energy or low protein intake reduces their growth and development and modifies their physical interaction with their environment, with unfavourable consequences for their cognitive development and subsequent learning and behaviour. Whether reduced activity in some societies is a social adaptation, as suggested by Rutishauser and Whitehead (Ref. 8), or is a direct response to low energy intakes, as INCAP data indicate (Ref. 9), the net result would seem to be the same.

Physical activity *per se* may have important nutritional consequences and a favourable effect on health. This is suggested by studies with experimental animals, showing that forced physical activity under conditions of food restriction results in better utilization of dietary protein and essential nutrients for purposes of tissue maintenance and growth (Ref. 10). In another study, small children who were being treated for protein-energy malnutrition grew better in terms of height and lean body mass when a programme of games was introduced to stimulate their physical activity (Refs. 9, 11). Thus, reduced physical activity in response to lowered energy intake may have additional untoward consequences for nutritional status as well as the separate metabolic effects of lower energy intake on nutrient utilization.

It must be recognized that the 1973 FAO/WHO allowances for human energy requirements (Ref. 1) are based largely on data obtained from Caucasian populations in industrialized countries. Although they provide the best available estimates of human energy requirements, their long-term health significance requires critical evaluation, particularly when a significant proportion of the adults in industrialized countries are overweight or obese to the point at which health is compromised. There is also evidence from the UK (Ref. 12) that energy intakes are now, on average, below those recommended by FAO/WHO in 1973.

The energy needs of adult populations in developing countries, on the other hand, may be greater than their energy intakes. Large segments of these populations are engaged in non-mechanized, physically demanding agricultural chores. There is evidence that if there were no constraints in relation to their diets and work output, their energy intakes would be greater and energy expended in activity would increase proportionately, and their energy requirements would be greater than those currently accepted (Ref. 13). Conversely, the socio-cultural demand and incentive for physical work is a very important and largely unmeasured factor, perhaps more important than food availability in many situations.

Energy requirements for adults also need to be explored further for populations in non-industrialized areas. The training effect of their work may allow many

labourers in those areas to remain physically fit and quite active at an age when the majority of people in industrialized countries become more sedentary, less fit, and, therefore, have lower dietary energy needs.

It is also clear that there are wide variations in the efficiency of energy utilization both among and within individuals (Refs. 4, 14), and, therefore, in their dietary energy requirements. How the human body regulates energy balance, and the quantitative significance of factors that affect energy requirements, deserve considerable futher study.

These various considerations make it difficult to judge precisely the applicability of the published estimates of energy requirements to populations of differing ethnic and environmental backgrounds. In addition, they pose difficulties for an understanding of the interrelationships between energy and protein requirements under various circumstances.

2. Assessment of Energy Expenditure and Energy Requirements

Energy expended in physical activity is highly variable among individuals, and it plays a major role in dietary energy requirements. The variability in energy expenditure is compounded by the complexity and limitations of the methods currently available to measure it. These can be grouped into three categories, each with its own shortcomings.

A first category would be the estimation of total energy needs based on dietary intakes and changes in body weight (Refs. 15, 16). This approach is applicable to population groups, with the limitations and errors inherent in dietary surveys. One of its major limitations is related to the evaluation of the energy intake of specific age and sex groups, because dietary surveys of the individual are more complex than those for the family, and it is not precise to extrapolate from the latter to each individual family member. Furthermore, body weight must be monitored over a period of time long enough to characterize the changes (or lack of them) in weight in conjunction with the mean energy intakes over the period of observation. This is further complicated by the marked seasonal variations in activity that characterize agricultural labour.

A second group of methods is based on time-motion studies coupled to measurements of the energy cost of the activities that are timed (Ref. 17). These methods involved a close observation of the experimental subjects, and unless the subjects are highly accustomed to the presence of observers—to the extent of no longer noticing their presence—they may change their working and activity patterns, thereby giving results that are not typical of their usual energy expenditure. It is easier to observe young children without

inducing behavioural changes, but there are not enough precise data concerning the energy cost of their activities to transform the time-motion information into energy expenditure. Moreover, there is insufficient evidence that energy costs measured in adults can be applied to children and merely adjusted for body weight. Instead, such a procedure could lead to large miscalculations, because the efficiency with which many activities are performed may vary in different age groups. A similar statement can be made in relation to persons from different socio-cultural backgrounds when the energy cost of activities is used as reported in the scientific literature, because experience and conditioning as a result of performing some activities more frequently may affect the efficiency and the energy cost of doing them.

The third group of methods is based on the continuous measurement of heart rate and its relationship to energy expenditure (Refs. 18, 19). In addition to the technological intricacies and costs of the equipment to monitor heartbeats in a free-living individual, these methods require the establishment of the heart-rate/energy-expenditure relationship for each individual under study, as the use of mean values for groups of individuals can lead to large errors due to the inter-individual variability. These relationships must be re-evaluated in individuals whose activity patterns, health, and nutritional status—among other conditions—change because physical fitness, body composition, efficiency in movement, etc., affect the relationships. This is particularly complex in very young children who must be taught to perform activities of various intensities for long enough to achieve a steady state. Furthermore, the relationship between heart rate and energy expenditure is neither linear nor consistent at low levels of energy expenditure, such as during rest or sedentary activities (Refs. 18, 20). This means that the resting energy expenditure of the individuals must also be measured, or assumed, in order to estimate the total energy expenditure.

In sum, although several investigators have used careful measurements of energy expenditure, the state of the art of measuring it, and thereby calculating energy requirements, is such that most researchers would find it very difficult to do. There is urgent need to evaluate critically and to simplify the existing methods for assessing energy requirements and expenditure and to develop new ones.

3. Sources of Dietary Energy

An issue of considerable nutritional and public-health importance concerns the type and level of intake of the major dietary sources of energy-yielding substrates. Increasing attention is now being given to the intakes of saturated and unsaturated fats and to the proportion of energy from complex carbohydrates, or from simple and refined sugars, in relation to chronic

diseases, including coronary heart disease, diabetes, and various forms of cancer (Refs. 21–23). In determining appropriate intakes of energy in populations within developing regions, it is necessary to consider the sources and levels of intakes of fat and carbohydrate that would be consistent with long-term health maintenance in these populations.

4. Practical Importance

Available knowledge concerning the energy requirements of human subjects at various ages and in different environmental conditions among populations throughout the world is highly unsatisfactory. Therefore, it must be recognized that a solution to the nutrition problems of developing countries requires much more reliable information on this fundamental aspect of human food needs. Planners and policy-makers need this additional information.

Protein

The major function of dietary protein is to furnish the body with an adequate intake and balance of essential (indispensable) amino acids and nitrogen for the synthesis of the so-called non-essential (dispensable) amino acids. These essential amino acids are used for the maintenance of body and tissue protein synthesis in the adult, and for net body protein gain during growth and development. While amino acids also serve as precursors for the synthesis of a number of physiologically active compounds, this need accounts for a relatively small proportion of overall daily protein requirement, although this clearly is of major physiological importance in maintaining normal body function.

Diets with a low protein concentration, or consisting of protein sources that are poorly utilized because of amino-acid deficiencies, limit growth and development in the young, and, depending upon other environmental variables, lead to increased morbidity and mortality. During development and periods of rapid growth, the requirements for dietary protein are high compared to the needs of the older child and young adult (Ref. 1). These changes in protein needs for the different age groups parallel those for energy requirements and the rate of total body protein turnover (Ref. 24).

According to present estimates of total body protein synthesis, it appears that dietary protein and energy intakes per kg of body weight required to support a given level of protein synthesis in healthy subjects may be similar in all age groups (Ref. 24). From these observations, new knowledge of the dynamic and quantitative aspects of whole body protein metabolism would be expected to provide a further useful basis for assessing the metabolic

significance of differences in protein requirements under various physiological and pathological states.

Estimates of protein requirements are largely based on studies of healthy adults, neonates, and young infants and of children recovering from earlier protein-energy malnutrition. Direct studies of healthy school-age children are limited, and a recent study of the pre-adolescent age group suggests that their protein needs may be higher than those currently recommended (Ref. 25). The available data for pregnant and lactating women are similarly limited and contradictory (Refs. 26, 27). Some of the uncertainty concerning available estimates is undoubtedly due to the limitation of the nitrogen-balance method as a means of assessing dietary protein adequacy and to the many factors that influence nitrogen balance (Ref. 28).

Another group for whom the data are limited is the elderly. The aging process involves progressive metabolic changes in various organs, leading to decreased functional ability and increased incidence of disease (Refs. 29, 30). Various age-related factors interact in a complex manner, and these may modify the level of nutrient intake and the efficiency of nutrient utilization by the body. The planning of nutritionally adequate diets for older people is currently based on extrapolation of data from studies of healthy young adults and, therefore, further investigation of the elderly is highly desirable.

1. Adaptation to Changes in Protein Intake

An understanding of the changes in body protein metabolism that occur with altered protein intake is basic to the critical evaluation of approaches used for estimating human protein and amino-acid needs under various conditions and in different population groups. This aspect of protein nutrition has been reviewed (e.g., Refs. 28, 31), but some important features of the responses of body protein metabolism to altered protein intake can be usefully emphasized here.

When a subject is given a low-protein, but otherwise fully adequate, diet, urinary nitrogen output decreases until a new steady-state in nitrogen excretion is achieved (Ref. 32). If protein intake is reduced below a minimum level, the subject will not be able to maintain nitrogen equilibrium and there will be a steady depletion of body protein. Associated with this condition are changes in body cell mass and an adaptive response characterized by increased recycling of amino acids and urea nitrogen, a decreased synthesis and fractional turnover of some secretory proteins, such as albumin, and a decrease in the size of the body's urea pool.

Inadequate dietary protein intakes have marked effects on the protein and

amino-acid metabolism of individual tissues and organs. The changes are multiple, they differ among the various organs, and depend upon the degree and length of the dietary restriction and the physiological and developmental stage of the subject when the inadequacy was first imposed. These various alterations in protein metabolism at the tissue and organ level are integrated into the total nitrogen economy of the intact organism. It is this total response of the organism that is of fundamental significance for the assessment of the adequacy of current approaches to the determination of protein requirements and evaluation of the nutritional value of dietary proteins.

Although present data about human subjects are limited, they are sufficient to indicate that total body protein and amino-acid metabolism respond to alterations in the level of protein, amino-acid, and energy intake via changes in body protein turnover, and/or by alterations in the efficiency of utilization and recycling of amino acids for protein synthesis (e.g., Refs. 33–35). These responses help to explain why the efficiency of utilization of dietary protein as measured, for example, by changes in the biological value (BV) and net protein utilization (NPU) of test proteins, is affected by variations in protein intake (e.g., Refs. 36, 37).

Knowledge of these metabolic responses provides support for the proposition that the determination of dietary protein requirements and assessment of dietary protein values are best approached by measurement of a function of body protein metabolism that is dynamic and of major quantitative significance in overall body protein metabolism and that also responds sensitively to graded levels of protein intake.

Studies from Nigeria conducted in the late 1950s (Refs. 38, 39), as well as recent reports from Taiwan (Refs. 40, 41) suggest that in countries where populations are chronically undernourished there may be adaptive changes in protein metabolism that may alter protein requirements relative to those determined for well-nourished individuals. In the Taiwan study, Oriental students fed a nitrogen-free diet lost less urinary N per kg of body weight than did Caucasian students (Ref. 42) previously studied in a similar manner. However, the former lost more nitrogen in their feces so that total obligatory losses were identical in both studies (Refs. 40, 42).

The studies by Nicol and Phillips (Refs. 38, 39) in Nigeria are particularly relevant to the important question about the nature and extent of adaptations to habitual low protein intakes. Adult males were found to be in positive nitrogen balance during short-term diet periods when given a rice-protein intake averaging 0.44 g/kg/day. At a generous protein intake providing 1.87 g/kg per day, a significant body-weight gain occurred in these same subjects, they were in marked positive nitrogen balance, and this was

accompanied by increases in serum albumin and hemoglobin. These observations suggest that the Nigerian subjects were more efficient in utilizing low intakes of rice protein than would be predicted from the studies by Kishi *et al.* (Ref. 43) in well-nourished Japanese men. Whether the increased efficiency was due to a favourable adaptive metabolic response to an habitual low protein intake, or to increased efficiency of nitrogen utilization known to be associated with tissue protein depletion, or to combinations of the two, cannot be determined. If this was a metabolic adaptation, its functional and health consequences in these Nigerian subjects receiving their usual diets require assessment. If more efficient utilization were the cause, the effect would last only until repletion was achieved. The physiological and biochemical consequences, including effects on disease resistance and work productivity, of any observed adaptation need to be evaluated. Nicol and Phillips (Ref. 38) also provided data on obligatory nitrogen losses in six Nigerian subjects. Applying the factorial approach of the 1973 FAO/WHO report to these data, a value of 0.6 g/kg is obtained as the safe protein intake. This latter value is not different from the 0.57 g/kg determined by the factorial method with data from healthy, well-nourished Caucasian males.

Clearly, there should be a further examination of these aspects of protein utilization in relation to requirements and health maintenance because of the major implications for the development of sound, rational dietary allowances for populations throughout the world.

2. Estimation of Nitrogen Requirements for Maintenance

Two major approaches have been followed for estimating the minimum physiological needs for total protein: (a) the factorial approach, and (b) the determination of the minimum nitrogen intake required to support body nitrogen equilibrium in the adult, or a given rate of growth and nitrogen retention in infants and children.

The factorial approach involves measurement of the losses of obligatory nitrogen via urine and feces when nitrogen intake is zero or very low and energy intake is adequate. Allowances for integumental and other miscellaneous nitrogen losses are added to obligatory losses. In the case of growth, pregnancy, or lactation, further allowances are made for body nitrogen gain, the nitrogen content of the fetus and its supporting tissues, and the output of nitrogen in breast-milk, respectively. This method is described in detail by FAO/WHO (Ref. 1).

It has been demonstrated in infants who have recovered from malnutrition (Ref. 44) and in healthy adult Caucasians (Refs. 37, 45) and Orientals (Ref. 43) that nitrogen retention or equilibrium cannot be obtained by providing

high-quality protein at a nitrogen level that is equal to the summated total obligatory nitrogen losses. Additional nitrogen is required, in part because there is a fall in the efficiency of dietary nitrogen retention as nitrogen intake increases from a markedly deficient level to an intake that approaches the requirement for maintenance and growth. A 30 per cent increase in nitrogen intake above total obligatory nitrogen losses was assumed by the 1971 FAO/WHO committee (Ref. 1) to be sufficient to meet this additional need. However, recent studies in adults (Refs. 43, 46) indicate that good-quality protein, such as egg or milk, is utilized less efficiently at maintenance-protein intakes than was suggested by FAO/WHO (Ref. 1). The data of Calloway and Margen (Ref. 45) suggest that an average increase of 38 per cent would be more appropriate, and for some subjects it may be as high as 50 per cent.

It must be emphasized, therefore, that precise estimates of the fall in efficiency of utilization by healthy subjects of all age groups of highly digestible, good-quality protein such as that in egg or milk are still lacking. For proteins of lower nutritive value, there is evidence that the fall in efficiency is progressively greater as the protein quality decreases (Refs. 36, 47).

In the second major approach, the nitrogen-balance response to graded intakes of protein within the area of submaintenance-to-maintenance nitrogen intake is determined for adults and for children over a range of intake levels that is close to those required for maintenance plus normal growth. This method is the most direct way of estimating protein needs, but suffers from the several limitations of the nitrogen-balance method discussed below. There are few adequate studies of this kind to provide estimates of even the minimum short-term needs for dietary protein from differing foods or combinations of food sources typical for the populations in developing areas, and long-term metabolic studies of nitrogen utilization are urgently needed, using diets of varying composition and quality that span the requirement range in adult men, women, and, where feasible and ethical, in younger age groups and pregnant and lactating women.

3. Nitrogen Balance and Organ Function

Most of the data available on protein and amino-acid requirements are based on results from metabolic nitrogen-balance studies. Useful information can be gained from nitrogen-balance determinations when they are carefully conducted, but for application to assessment of protein and amino-acid requirements it is important to recognize that this technique has the following significant limitations.

(a) Body nitrogen equilibrium does not necessarily reflect a steady-state of organ protein metabolism, or of nutritional status, because it fails to

reveal alterations in the quality and distribution of tissue metabolism and protein content within the body.

(b) In addition to the well-recognized cumulative errors in estimating nitrogen balance, it is also difficult to measure quantitatively all of the routes of nitrogen loss from the body. Furthermore, loss of nitrogen via one route may be compensated for by changes in the losses of nitrogen via another (Ref. 41). Therefore, unless all routes of nitrogen loss are measured, erroneous conclusions may be drawn from *apparent* nitrogen-balance values, and, in consequence, requirements underestimated. Most of the nitrogen-balance data in the literature have involved only measurement of urinary and fecal losses. It would be valuable to have reliable data on the extent of integumental and miscellaneous nitrogen losses for both children and adults under usual conditions of living, and where increased sweating in hot climates may alter total nitrogen needs.

(c) Factors other than the level of intake and nutritional value of dietary protein affect nitrogen balance, and these must be considered in evaluating data from nitrogen-balance results. These factors include level of energy intake and expenditure, composition of the diet, and prior nutritional state of the subject, as well as physiological and pathological states, including intercurrent infections. The significance of the higher dietary fibre intakes, characteristic of the diets in developing regions, for fecal nitrogen (and energy) losses in relation to protein and energy requirements must be explored.

It is now becoming more clear that nitrogen-balance determinations alone do not provide an adequate measure of dietary protein need, or of changes in nutritional status. Measurement of nitrogen balance is simply an overall summation of body nitrogen change, and therefore may conceal metabolic alterations related to protein intake that could result in pathological states. For example, during a long-term metabolic study of young men receiving egg protein at a level of 0.59 g/kg body weight/day (Ref. 46), increases occurred in serum aspartate and alanine amino-transferase activities, and these changes were reversed by increasing dietary protein intake. Although the precise significance of these elevations in enzyme activity is not known, it was assumed by the investigators to reflect undesirable changes in liver function, and support for this was obtained by isoenzyme measurements and changes in other indices of body protein metabolism. Furthermore, these were not observed in similar long-term metabolic studies with beef protein or with a well-processed soy-protein isolate given at intakes equivalent to about 0.8 g protein/kg/day, and the diets supported body nitrogen balance in nearly all of the young men studied (Ref. 48).

Particularly important in the context of estimating human protein

requirements is the critical need to develop functional measures of protein nutritional status. This will require more study of the dynamic and biochemical aspects of body protein and amino-acid metabolism, both in animal models and in human subjects.

4. Nitrogen Balance and Nutritional Value of Dietary Proteins

A primary metabolic need that must be fulfilled by dietary protein is the provision to the organism of an adequately balanced mixture of essential amino acids. Present estimates of the essential amino-acid needs of infants and adults do not reveal any clear-cut differences in the *pattern* of amino-acid requirements for the two age groups. Because the estimates for each amino acid are imprecise, perhaps no better than $\pm$ 50 per cent (Ref. 49), it is not possible to conclude from available data that the essential amino-acid *pattern* differs with developmental age, except for the neonate. Nevertheless, infants and growing children require a higher intake of amino acids per unit of body weight than is necessary for the adult.

Current data also indicate that the requirement for total essential amino acids declines more rapidly with age than does the need for total dietary nitrogen. Hence, it has been estimated that the infant requires approximately 37 per cent of total nitrogen in the form of a balanced mixture of essential amino acids (Ref. 1). For the healthy adult, essential amino acids should comprise 15 per cent of the total nitrogen requirement. Although these estimates are not precise, they do indicate that the nitrogen and amino-acid requirements change at different rates with age. The general view is that age determines the nutritional value of a dietary protein source for an individual, but the precise nature and extent of the age-dependent relationships is not known.

Comparative studies of the nutritive value of differing protein sources are required, using the same sources in subjects of different ages, and using critical and, ideally, identical methods of nutrition assessment. This will be necessary before a definitive statement can be made regarding the quantitative impact of age on the value of food proteins to meet human needs. This is particularly important in reference to an evaluation of whether the safe level of protein intake, adjusted for NPU, is adequate for young children when the protein is derived from customary foods. Although there are some data available, it is necessary to obtain more information on the wide range of diets characteristic in many areas of the world.

The methodology for the biological assessment of the nutritive value of dietary proteins has been reviewed recently by several authors (Refs. 28, 50–52). There is still controversy regarding the choice of approaches for

determination of the nutritional value of proteins, but it is clear that assays involving only a single level of a test protein are inadequate. The protein efficiency ratio (PER) is an example of this latter approach. Assays involving more than one level of test protein and, in particular, those that determine response (weight gain or nitrogen retention) to multiple doses of a test protein are necessary for the precise determination of dietary protein value. An additional concern relates to the quantitative applicability of data obtained in assays using experimental animals, especially the rat, to humans. Unfortunately, most earlier studies of dietary protein value in adult man have involved the determination of biological value (BV) or net protein utilization (NPU). With either method, test proteins are traditionally studied at low levels of total protein intake, where metabolic adaptation has occurred, and do not necessarily provide an adequate prediction of the capacity of the protein to meet physiological requirements.

Few studies of the nutritional value of food proteins in human subjects have utilized multiple levels of test protein intake. Even when this approach has been used, the experimental protocols have varied among the laboratories, making it difficult to compare estimates of protein nutritional value among different experiments. There is a need for satisfactory, standardized approaches to the clinical evaluation of protein quality in humans.

It is also important to resolve the uncertainties surrounding the applicability of findings on the nutritional value of food proteins in young adults to pre-school-age children and elderly subjects. Furthermore, because of the practical and ethical problems of undertaking protein quality studies with children, it is of considerable importance to define the manner in which feeding studies in adults should be conducted to give values that best predict the nutritional value of food proteins for younger age groups.

The determination and significance of protein quality in humans at various ages, and particularly in relation to usual or local diets, is essential. Most studies of protein quality have involved the use of carefully designed experimental diets in which the test protein source was incorporated. However, the source, type, and level of carbohydrate and fat, as well as the mineral and vitamin content of the local diet, may affect energy and protein utilization. In order to determine the capacity of local diets to meet protein needs, an effort must also be made in clinical studies to examine diets based on usual foods in the manner in which they are prepared and consumed rather than on non-indigenous protein sources. This is not only important for purposes of assessing the adequacy of current diets, but is also significant in evaluating the possible nutritional and health benefits that can be expected from amino-acid fortification of local diets and from plant-breeding programmes.

5. Protein-Energy Interrelationships

Because individuals do not eat protein or dietary energy as such, but rather the foods that supply them, attention must be paid to the extent to which foods and the diets that comprise them supply the needed proportion of protein when the daily energy needs are met. An evaluation of the appropriate protein energy ratio is complicated by the variation in energy and protein needs caused by individual variations in genetic characteristics, body composition, physiological state, and physical activity. This becomes even more critical when pathological factors such as infections appear to increase protein needs relative to those for dietary energy (Ref. 53).

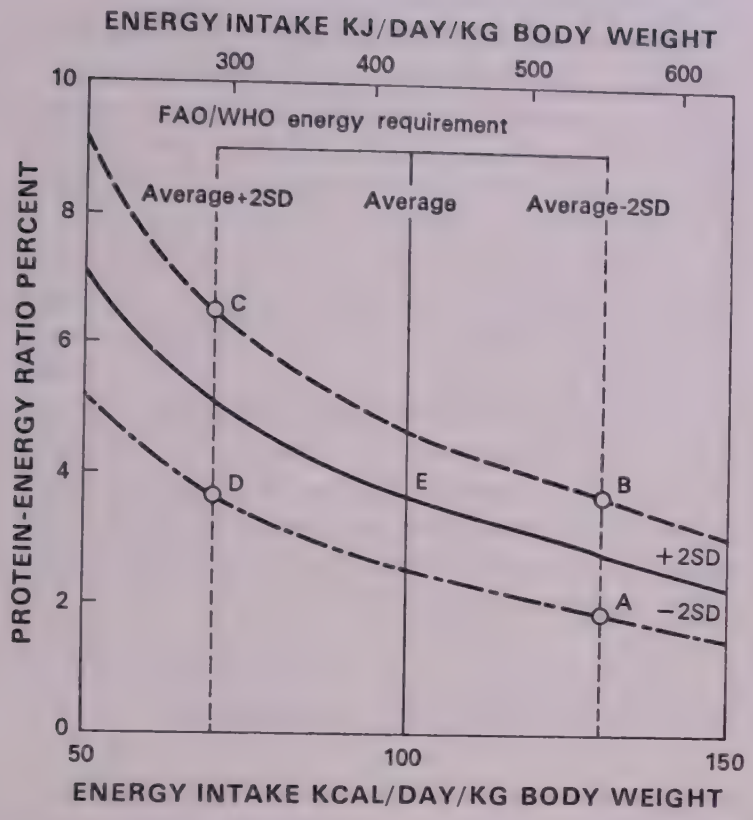
An early attempt to deal with the quantitative relationships between protein and energy requirements for healthy individuals was the concept of net dietary protein calories expressed as percentage of total calories (NDpCals%) (Ref. 54). This was derived from the age- and sex-specific mean requirement for protein and energy. In evaluating the capacity of a diet to meet this average requirement, correction is made for the NPU of the diet, and the result is expressed as the percentage of total calories furnished by available protein calories.

In public-health activities, measurement of this simple relationship between average requirements for protein energy and the mean estimate of the efficiency of dietary protein utilization is limited because each of these components varies (Refs. 55, 56). Clearly, the proportion of available protein calories in a diet must be sufficient not only for the individual whose requirements for both are at, or below, the average values, but also for those individuals whose protein requirements are above the average for the population It is necessary to consider this because there is little or no correlation between protein and energy needs expressed per kg of body weight in adults (Ref. 57).

Figure 2.1 taken from Payne (Ref. 55), and as published in the report of the 1975 FAO/WHO informal gathering of experts (Ref. 58), considers applications of the recommendations of the 1973 report (Ref. 1). Point E in the figure corresponds to the mean P/E ratio for children 1–3 years of age, whereas point C represents the percentage of available protein calories to cover approximately 97.5 per cent of the entire population on the basis of the following assumptions:

(a) the mean and standard deviations of protein requirements for children 1–3 have been adequately established in the 1973 FAO/WHO report (Ref. 1);
(b) protein availability at requirement levels is adequately predicted from the NPU values used; and
(c) protein and energy requirements are normally distributed.

FIG. 2.1.



The solid vertical line describes the average energy needs of children 1–3 years old. The vertical broken lines describe the estimated limits of the variability of the energy requirement (±SD). The solid curve represents the dietary protein concentration required to meet average protein needs at the specified caloric intake. The broken curved lines represent the limits of variability (±2SD), the upper representing the safe level of protein intake. (Source: Payne, Ref. 55).

As discussed in foregoing sections, none of these assumptions have received careful validation, and so the practical significance of the values shown in Fig. 2.1 may be questioned. However, as breast-milk from well-nourished mothers provides 7–8 per cent protein calories, and babies grow well providing they receive sufficient milk, point C would be appropriate for this group of young children. However, in the specific context of populations where acute and chronic infections are endemic, it should again be stated that data on which the estimates are now based have been obtained from healthy subjects. As Beaton and Swiss (Ref. 57) have pointed out, the effects of stress from infections and other factors known to be highly prevalent among the populations of developing countries need to be determined in relation to the adequacy of the ratios for dietary planning illustrated in Fig. 2.1.

The 1973 report (Ref. 1) attempted to identify reliable experimental and field data to indicate the percentage of protein calories needed in the diets of various age groups and found that such data as exist are exceedingly limited and inadequate for the purpose. Calloway (Ref. 59) has provided direct experimental evidence in normal, healthy adult Caucasian subjects, in the confined environment of a metabolic ward, that 5 per cent of energy as egg protein was inadequate to maintain nitrogen balance in six subjects, but that 7 per cent appeared to be adequate. Obviously, this would be influenced by the level of activity established by, or for, the subjects. The results, however, provide little information about the percentage of protein calories needed by populations living under conditions of high environmental stress, or whether under such conditions, with the usual diets, the percentage of protein calories needed differs from that appropriate for healthy populations in developed regions of the world. More recent data have been obtained from studies of the amount of high-quality protein required by healthy young adults to maintain protein nutritional status, and the results are shown in Fig. 2.2. These data suggest that higher P/E ratios may be more appropriate for populations living in developing regions of the world.

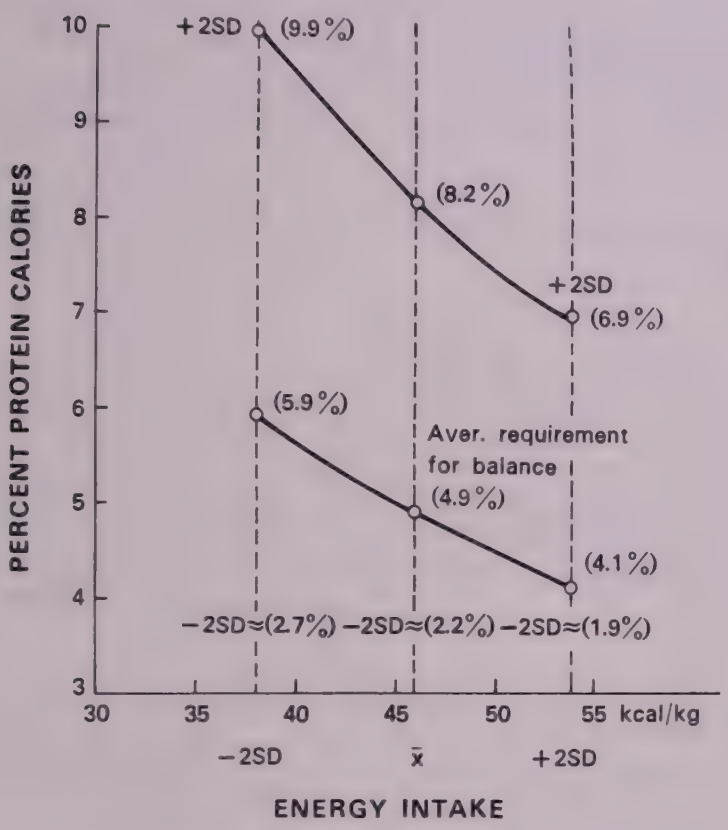
6. Statistical Considerations and the Development of a Safe Allowance for Protein and Essential Amino Acids

The recommended allowances for protein, and estimates of the requirements for individual essential amino acids, as developed by various FAO/WHO expert committees, are intended to apply to all healthy populations of the world. Many national recommended allowances are derived from the FAO/WHO standard. Yet it must again be emphasized that current allowances are based on limited data from small and possibly unrepresentative samples of persons. However, appropriate allowances cannot be formulated for population groups until the variation in requirements among apparently similar individuals has been measured in a systematic and critical way using valid criteria.

The most fundamental variation in requirements is that due to individual differences. The variation is the result of both inherent genetic potential and the modifying effect of environment on the expression of that potential. Biological variation in the requirements of healthy individuals free of stress may be normally distributed in a statistical sense, but many factors can skew this distribution or cause individuals to fall outside of it. The determination of normal variation in protein and amino-acid requirements necessitates identifying and separating methodological and environmental variables from those attributable to genetically based, individual differences.

Estimating a dietary protein allowance for a population involves two separate problems. First, the mean requirement for that population (PR_m) must be

FIG. 2.2. Net dietary protein calories percentage for N-balance with high quality protein when energy needs of MIT students are met (egg, 7; beef, 7)



estimated. For adult subjects, the usual approach is to determine the relationship between nitrogen balance and protein (nitrogen) intake and to define PR_m as the minimum protein intake necessary to support zero nitrogen balance or nitrogen equilibrium.

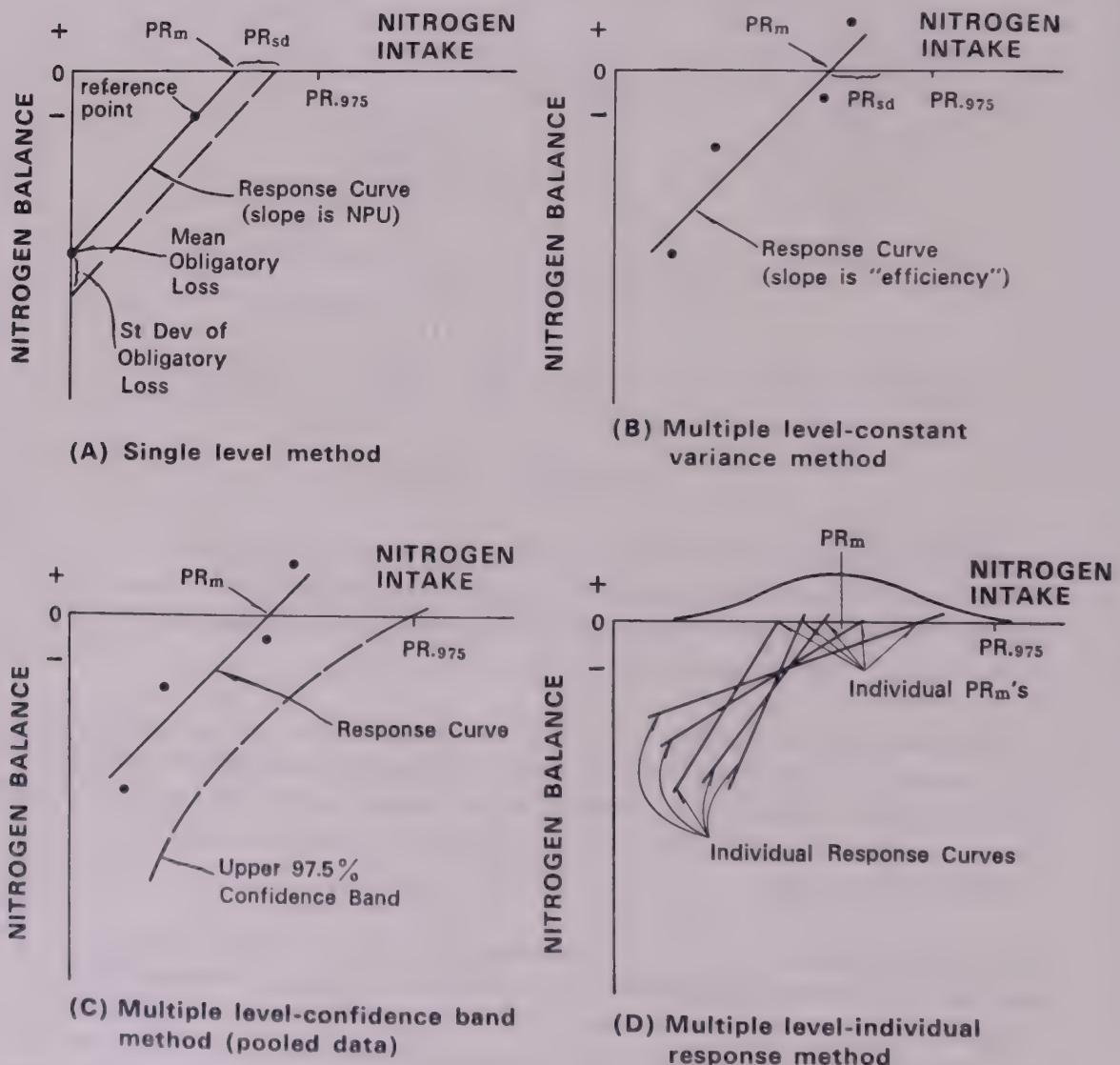
The second problem involves estimating the variability in requirement within the population; the symbol PR_{sd} is used to indicate the standard deviation of the population's protein requirement. These two quantities, PR_m and PR_{sd}, can be used to predict PRâ, the protein allowance for a fixed percentage of the population group.

Four methods can be used to evlauate nitrogen-balance data in relation to assessment of dietary allowances (Ref. 60). These methods, schematically depicted in Fig. 2.3, have been discussed in detail by Rand *et al.* (Ref. 60). In summary, however, an application of these methods is illustrated in Table 2.2, using data from a typical nitrogen-balance experiment in young men consuming graded levels of beef protein (Ref. 60). The succession of the four

methods reflects an increasing consideration of both the complexities of human protein metabolism and of the sources of variability inherent in the process of determining requirements of individuals and populations.

The methods differ in that they successively make fewer assumptions and take into account progressively more of these sources of variability and recombine them in a "worst-case" fashion in calculating a protein allowance figure. Hence, in general, each method produces a larger allowance figure than the

FIG. 2.3. Four methods for estimating protein allowance from nitrogen-balance data



PR_m = mean protein requirement, PR_{sd} = standard deviation of protein requirement, $PR_{0.975}$ = 97.5 % protein allowance. See text for details. (Taken from Rand *et al.*, Ref. 60.)

TABLE 2.2. Estimates of dietary protein allowances using each of four methods and based on N-balance data in young men receiving graded intakes of beef protein

Method	Mean requirement	Allowance
	mgN/kg/day	
Single level	71	91
Multiple level:		
—Constant variance	82	104
—Confidence band	82	110
—Individual response	83	121

The four methods are depicted in Fig. 2.3. (Adapted from Ref. 60.)

preceding one and requires a larger sample to avoid overstating the variation. At the same time, each method, by specifying more completely the sources of error, indicates specifically how the allowance estimate can be made more precise (when dealing with biological variability) and smaller (when dealing with experimental error). It appears that the third method is suitable for application to the analyses of nitrogen-balance studies, given the maximum sample sizes that are now feasible.

For purposes of estimating the appropriate range of requirements, more data on the nature and reproducibility of the nitrogen-balance response to various protein sources within the same individuals will be required. These considerations underscore the need for further critical statistical investigations of the approaches to be taken in the estimation of nutrient requirements and the application of such data to population groups.

III. THE NUTRITIONAL CONSEQUENCES OF ACUTE AND CHRONIC INFECTIONS

General Effect on Appetite and Nutrient Intake

In general, infections cause anorexia, and consequent reduced intakes of protein and energy. The extent to which appetite is depressed depends on the type and severity of the illness and on the individual, and it may be confounded by vomiting. Alterations of dietary intake, particularly withdrawal of solid foods, during infection are also almost universally practised. Table 3.1 summarizes results in children for whom food intake was measured during and following various illnesses. Clearly, the degree and duration of altered food intakes vary considerably, but these data emphasize the profound and marked reductions in food consumption that occur in a significant proportion of the cases studied.

Socio-cultural factors also contribute to alterations in food intake, depending on the significance of disease within the culture. Traditions, taboos, and beliefs about appropriate therapy account for (a) suppression or reduction of food intake; (b) alterations in dietary compositions; and (c) addition of substances not customarily present in the diet, such as medicinal plants and drugs. The nutritional consequences of dietary changes of this nature are often marked. Other alterations in food intake during and after illness are the direct consequences of the effects of localized or systemic infections on host metabolism, as reflected in anorexia, vomiting, and diarrhoea, and also in impairment of masticating or swallowing.

These several groups of factors—metabolic, symptomatic, and cultural—that interfere with food intake are of paramount importance in determining the outcome of infection and the overall nutrition of individuals and the growth of children in developing societies. Therefore, dietary recommendations must take into account these negative and interactive effects of nutrition and infection.

TABLE 3.1. Effect of infections on food intake

	Days duration of depression of caloric intake				Days to average out caloric intake after infection*		
	1	1+	Average	Range	No. of episodes	Average	Range
Respiratory infections	24	68	6	1–19	63	15	1–19
Diarrhoea/ dysentery	1	11	6	2–16	12	20	4–40
Fever of unknown origin	9	21	4	1–16	20	13	2–25

(From D.S.M. Pereira, Nutrition Department, Christian Medical School, Vellore, South India)
*Diminished intake during infection plus days of recovery.

Even though the interactions of infection, dietary intake, and metabolism are important, it can be concluded that for well-nourished subjects living in sanitary environments, there is rapid return to normal health and well-being. The customary care, diet, and treatment of children of upper socio-economic groups usually correct nutritional deficiencies consequent to infection, and rapid recovery of body weight occurs after illness in well-nourished children (Ref. 61).

The situation among less-privileged children in most developing countries is quite different. To begin with, diets are based on bulky, starchy foods with a low concentration of total protein, of relatively poor nutritional value, and of low caloric density. Thus, it is often difficult or impossible to correct protein and energy deficiencies by simply increasing the intake of the traditional diet. At weaning, the child must adapt to an abrupt change from its diet of maternal milk to a high-fibre, high-bulk rural diet of lower nutritional value. This period of adaptation usually is associated with an increased frequency of infection and ensuing clinical manifestations, particularly diarrhoea.

Anorexia explains only part of the negative nutrient balances that are associated with infection. In relation to body nitrogen balance, other factors are the metabolic changes that occur in response to infection, leading to increased nitrogen excretion, muscle wasting, altered organ function, and the diversion of ingested protein to support the host body's defense processes (Ref. 61).

In the already depleted individual, the worsened nutritional status induced by infection adds further to the morbidity and mortality from infections in malnourished individuals. In fact, malnutrition and infection interact

synergistically not only because of the effect of infection on nutritional status, but also because the frequency and severity of infection are greater when resistance is impaired by nutritional deficiencies (Ref. 62). Not all infections influence metabolism and food utilization to the same degree, and therefore in the following section a summary is made of the major nutritional consequences of the diseases that are important to the populations in developing countries.

Specific Effects of Different Infections

1. Gastrointestinal

Certain infections specifically affect the gastronintestinal tract and lead to diarrhoea and intestinal malabsorption. Infants and pre-school children are particularly at risk. It is established that children in environments associated with protein-energy malnutrition have atrophy of the gastrointestinal villi and mucosa (Refs. 63, 64) and an increase in flora (Refs. 65, 66) and free bile acids in the small intestine (Ref. 67). This altered gastrointestinal ecology, as well as varying degrees of gastrointestinal digestive dysfunction (Ref. 68), have been reported in both children and adults from rural and urban low socio-economic groups in non-industrialized countries. Such changes seem to be related to the high incidence of chronic, non-specific diarrhoea and mild to moderate malabsorption observed within these populations (Ref. 69).

Nearly all diarrhoeas involve some degree of cell injury, with loss of fluid and nutrients and reduced nutrient absorption. Furthermore, they are often accompanied by fever and anorexia, and require a period of days or weeks for convalescence. However, there are differences in the ways in which infectious agents interact with the host to induce diarrhoea (Ref. 70).

Nitrogen losses via the diarrhoeal stool can be high (200–400 mg/kg/day), and amount to 30–40 and sometimes as much as 60 per cent of protein intake in severe cases (Ref. 71). Similarly, high fecal energy losses are observed (Ref. 71). The magnitude of fecal losses of water and electrolytes in severe diarrhoeal disease can also be considerable (Ref. 72).

Infections involving the gastrointestinal tract, especially in combination with malnutrition, may induce secondary intolerance to complex or simple carbohydrates. For example, unabsorbed lactose from a milk-based diet can, in some susceptible individuals, aggravate or precipitate diarrhoea, thus further increasing the loss of energy and nutrients, water, and electrolytes. There is some evidence that fat and protein absorption are also reduced in populations with frequent episodes of diarrhoea.

It was found that a significant proportion of healthy adult males from rural communities in the lowlands of Guatemala absorbed lesser amounts of the nitrogen and energy present in a rural Guatemalan diet providing 2,800 kcals than did a group of Guatemalan soldiers eating the same diet but living in a more sanitary environment (Table 3.2.).

TABLE 3.2. Percentage absorption of nitrogen and calories from diets of varying fibre content by Guatemalan and U.S. males

		Guatemalan corn-black-bean diet	Egg formula fibre-free diet	Egg formula diet with oat bran[1]
Rural lowland Guatemalan males 15–45 years old	N[2] (24)	% 73 ± 10	% 76 ± 4	% —
	Energy[3]	91 ± 4	95 ± 3	—
Rural lowland Guatemalan males after 20–23 mos. military service	N (13)	85 ± 5	—	—
	Energy	92 ± 2	—	—
U.S. male university students	N (6)	69 ± 2	87 ± 3	86 ± 4
	Energy	89 ± 2	97 ± 1	94 ± 2

1. 0.6gm/kg body weight
2. Apparent protein digestibility, % dietary N − fecal N/dietary N × 100
3. Digestible energy, % = dietary kcal (bomb) − fecal kcal (bomb)/dietary kcal (bomb) × 100.

Preliminary results from an experiment in which rural Guatemalan adults ate a highly absorbable, low-fibre egg formula or a Guatemalan rural diet predominantly comprised of corn and black beans for consecutive periods of fifteen days suggest that the reduced gastrointestinal absorptive capacity of these subjects at the time of study was unrelated to the kind of diet consumed; absorption of nitrogen and calories was similar in these subjects during the consumption of either diet (Table 3.2), but was lower than absorption of the egg-formula diet by healthy North Americans. It is noteworthy that the identical corn-and-black-bean diet was also poorly absorbed by the North American subjects. Addition of oat fibre to the egg-formula diet had little effect on its absorption by the latter subjects.

The effects of the environment in which these subjects live, as well as the adaptation of the gastrointestinal tract when they consume other kinds of diets, need to be explored further. It is also important to evaluate the effect of their gastrointestinal flora on food absorption. Theoretically, it is possible that intestinal bacteria may compete for part of the food ingested to fulfil their own metabolic needs, thus decreasing the amount of nutrients available for absorption.

In summary, infections affecting the gastrointestinal tract cause water, electrolyte, energy, and nitrogen losses and impaired absorption of nutrients. The extent varies with the severity of the illness, and, in long-standing infections, these losses can lead to severe nutritional deficiencies.

2. Infections of the respiratory tract

This group of illnesses is as common as, or even more prevalent than, the diarrhoeal diseases (Ref. 73). The infections in question range from "colds" to severe otitis media, bronchitis, or bronchopneumonia. They can also be associated with systemic manifestations such as fever, anorexia, malaise, and general weakness.

Usually, infections of the upper respiratory tract are milder and of shorter duration than are diseases of the lower respiratory tract. However, even upper respiratory infections can be associated with weight loss and retarded growth, particularly during the first two years of life (Ref. 73). This negative effect on nutritional status is apparent primarily in children already suffering from some degree of protein-energy malnutrition. In these children, duration of the respiratory infection and recuperation are both longer. Also, respiratory diseases tend to occur as sequelae to viral illnesses such as measles. In field observations in developing countries, 90 per cent of the measles cases in children were seen to be complicated by either diarrhoea (33 per cent), bronchopneumonia (16 per cent), or both (41 per cent). The case fatality in this situation was high (Ref. 73).

Whooping cough also has a particularly prolonged effect on nutritional status and has been found to be responsible for an appreciable number of deaths among malnourished children (Ref. 74). About one-quarter of poor rural children suffer a weight loss greater than 5 per cent of their pre-illness weight. Under these circumstances, small infants and children have been reported to lose an average of about 500 grams during pertussis. Part of the effect is due to a marked reduction in food intake consequent to anorexia and coughing (Ref. 74), and many of the metabolic alterations are induced by the infectious process.

Pharyngitis and tonsillitis of either bacterial or viral origin, and glossitis and thrush caused by viruses or fungus all exert a marked effect on host nutrition. This is partly because it becomes too painful for the child to swallow food. Otitis media not only markedly affects host nutrition by rapidly inducing severe negative nitrogen balance and energy deficits, as do other infections, but also it is often accompanied in its early phases by diarrhoea. Otitis media may later become chronic, with recurrent episodes of fever and pain.

3. Other disorders

Although some rickettsial and certain viral diseases may cause exanthemic or hemorrhagic diseases of considerable severity and consequence, they generally occur in populations living in particular circumscribed ecosystems. The problem of major public health significance in the children of developing nations pertains to those viruses that cause the exanthemas of childhood: measles, rubella, chicken-pox, roseola infantum, exanthem subitum, enteroviruses, and adenovirus exanthemata. Although mortality may be quite low with rubella and chicken-pox (Ref. 74), all of these diseases induce negative nitrogen and energy balances and weight loss, and measles has an especially profound effect on health.

Tuberculosis. This illness is the most typical example of a common infection that runs a protracted course. In addition to producing chronic cachexia in adults, in children it leads to severe nutritional deficits that may become so far advanced that kwashiorkor is precipitated before the patient is suspected of having a tuberculous infection.

Hepatitis and Gram-negative sepsis are accompanied by additional severe metabolic consequences. In the latter, increased output of catecholamines, an accumulation of triglycerides in the serum, and a fall in serum inorganic phosphate levels have been observed.

Parasitic diseases. Nutritional responses are influenced importantly by the type of parasite and the severity of the lesions induced. Malaria is of major nutritional importance because of its potential world-wide distribution, its acutely febrile nature (which produces all of the fever-related consequences of other infections), its hemolytic effects, and its occasional secondary detrimental aftermath of excessive hemoglobinemia. Also, malaria can enter a prolonged, chronic phase with intermittent relapses and long-term nutritional deficits. Because of this synergism with malnutrition, extremely high child mortality rates occur in countries where malaria is holoendemic (e.g., the Gambia, Malawi), with increased mortality during the transmission season. A striking fall in overall child mortality has occurred where malaria has been eradicated (e.g., Guyana).

Other systemic parasitic infections can lead to cellular destruction or fibrosis in key organs and tissues. These lesions can, in turn, initiate secondary nutritional deficits. Parasites such as *Schistosoma haematobium* in the urinary bladder and intestinal nodules from *S. mansoni* can result in chronic blood loss and iron deficiency, as well as in impaired ability of the intestine to absorb lipids and other nutrients. Severe protozoan and helminthic infections

of the gastrointestinal tract, individually or in combination, can significantly reduce intestinal absorption and cause diarrhoea (Ref. 75).

Infection in Relation to Metabolism of Nutrients

The species of invading microorganism helps to determine the nature and magnitude of nutritional sequelae in the host. All systemic, and many localized, infections initiate a sequential panoply of relatively stereotyped, common metabolic responses (Ref. 61). Fever, proportional to its severity, accelerates oxygen consumption (Ref. 76). The increase in basal metabolic rate heightens the need for metabolizable sources of energy for consumption by all body cells. This need is generally met, during acute stages of illness, by deriving energy from stores present within the body. Unfortunately, as detailed above, the concomintant presence of anorexia during infections generally reduces the intake of dietary sources of energy, protein, and all other important nutrients. It is noteworthy that infections without overt fever or clinical symptoms also cause anorexia and precipitate the stress response, although some elevation of body temperature may be associated, whether or not detected.

During infectious illness body cells depend, to a major extent, on carbohydrate as the principal substrate for meeting their energy needs. Glycogen stores are utilized, and gluconeogenesis is accelerated, primarily in the liver. To maintain a source of glucose there is an increased uptake of gluconeogenic amino acids from the plasma by the liver where the carbon skeletons are used for the *de novo* synthesis of glucose. The nitrogen atoms released during this process are converted to urea and ammonia, and subsequently excreted via the urine. A major source of the amino acids is skeletal muscle protein, and these amino acids are released into plasma as a direct consequence of an accelerated rate of muscle protein breakdown (Ref. 77).

The body will normally respond to simple starvation by stepping up the release of fatty acids and synthesis of ketone bodies in the liver. The ketones then serve as important substrates for use in meeting cellular energy needs. This ketogenic process, which diminishes protein catabolism during simple starvation (Ref. 78), either fails to occur, is delayed, minimized, or actively suppressed by some yet unknown mechanism during acute febrile infections (Ref. 78). More information is needed about ketogenesis or its suppression in a variety of clinical infections. Although children may become acidotic and excrete ketones in the urine during infections, they may also die of protein depletion even though considerable body fat is still present.

As a consequence of accelerated gluconeogenesis and altered lipid

metabolism, the proteins of skeletal muscle, rather than the fat depots, serve as the primary sources of the extra metabolizable energy needed during acute infections. This process leads to marked muscle wasting and debilitation with continued infection.

Amino acids derived through the catabolism of skeletal muscle are used for other purposes related to host defense as well as for gluconeogenesis. During acute infections, additional phagocytic cells must be created, the lymphoid system must be activated, immunoglobulins must be synthesized, and other proteins such as the "acute phase" reactant group of serum proteins, as well as a wide variety of intracellular enzymes, must also be produced. Indeed, every known defense mechanism used to protect against microbial invaders is ultimately dependent upon the ability of body tissues to synthesize new protein molecules, and these needs can only be met by an adequate availability of free amino acids.

Thus, during acute infections, sources of amino acids within muscle and other tissues are utilized in two key roles: to permit accelerated gluconeogenesis, and to allow synthesis of vital new defensive proteins. Their use in gluconeogenesis is wasteful from the standpoint of body nitrogen and amino-acid economy because essential amino acids lost by oxidation can only be replaced by the diet.

In protein-calorie malnutrition commonly associated with prolonged infections or other serious illnesses, host defense capabilities are likely to be weakened. Various manifestations of cell-mediated immunity are the first to be affected (Ref. 79), but homoral immunity is also impaired by almost any type of severe nutritional deficiency (Ref. 79). Epithelial barriers and tissue integrity to microbial invasion may also be affected. Opportunistic infectious illnesses may develop, and primary infections seem to become more severe.

Host metabolic responses to acute infection are influenced by hormonal controls as well as by the availability of substrate nutrients (Ref. 61). An accelerated output of adrenal glucocorticoids, mineralocorticoids, and catecholamines has been detected (Ref. 80). The thyroid hormones are de-iodinated rapidly, the pancreatic islets increase their output of both insulin and glucagon. Growth hormone, ACTH, and TSH are released from the anterior pituitary, and the posterior pituitary may secrete antidiuretic hormone in an inappropriate manner, especially during infections located within the central nervous system. Single body cells engaged in phagocytic activity release kinins, prostaglandins, and serotonin, all of which have localized as well as more generalized effects. These cells also release mediator substances that stimulate such diverse host responses as leukocyte release (marrow); fever (hypothalamus); altered trace element absorption (intestine); and

accelerated cellular protein synthesis (liver).

These hormonal and mediator effects have been documented, and must be recognized as important basic phenomena during acute infections because they influence carbohydrate, fat, protein, mineral, and electrolyte metabolism.

However, hormonal responses are not easily manipulated, and the more useful therapeutic approach to supportive care during infectious illness would be to focus upon the potential ability of a treatment regimen to provide or regulate the availability of appropriate substrate nutrients. This nutritional approach to supportive therapy requires an understanding of needs for protein and energy during and after acute infections, as well as for fluid, electrolytes, minerals, and a large variety of trace micronutrients.

Detailed information about host metabolic, nutritional, and endocrinal responses during infections has generally been obtained either from young adult patients experiencing an acute infection, or from laboratory animals studied during the course of experimentally induced infections. Fewer details are known about infections in infants and children, or about chronic infections in adults. Little is known about the progression of metabolic and nutritional events when an infection enters into its subacute or chronic stages, but these phases of disease may cause nutritional problems of different kinds.

Studies in infants and children are especially important, because they are the at-risk groups with the highest mortality associated with infection-nutrition interactions. These studies are made especially difficult because of the superimposed nutrient requirements for growth, and because of differences in body composition, immune status, and metabolic maturation among children in different age ranges (neonates, pre- and post-weaning infants, and pre-school and school agers). Each of these ages has its own specific nutritional needs and unique susceptibilities to different kinds of microorganisms.

Because of the presence of anorexia during acute febrile infections, and the accelerated expenditure of body nutrient stores, it is generally impossible even under hospital conditions to prevent the depletion of body nutrients. Indeed, cumulative balance data indicate that: (a) body nutrient pools become maximally depleted only after an acute episode of illness has terminated, and (b) depletions may persist for long periods despite an apparently complete clinical recovery.

As mentioned previously, the depletion of body nutrient pools leaves the host especially vulnerable to secondary or superimposed infections. These infections will then produce an additional wastage of body nutrients, and the downhill spiral of infection-malnutrition-infection proceeds. In order to

prevent or minimize these consequences, body nutrient pool deficits must be repleted without delay after an acute infectious process has been resolved. This requires the provision of adequate amounts of extra dietary nutrients to permit the full restoration of body nutrient stores, and, in the case of children, permit recovery of body weight.

Even though it may be impossible, or even unwise, to prevent deficits from occurring during an illness, the disappearance of fever and anorexia provides a special time for increasing the intake of nutrients. This attempt may be helped by a post-illness hyperphagia that may occur in some patients (Ref. 81). Far too little emphasis has been placed on the therapeutic use of this "nutritional window" that opens as fever and anorexia disappear. This opportunity should be exploited in future investigations to determine the optimal quantities and qualities of nutrients that should be supplied, and further, the speed with which the process of nutrient repletion can be accomplished.

IV. NUTRIENT REQUIREMENTS FOR CATCH-UP GROWTH AND TISSUE REPLETION

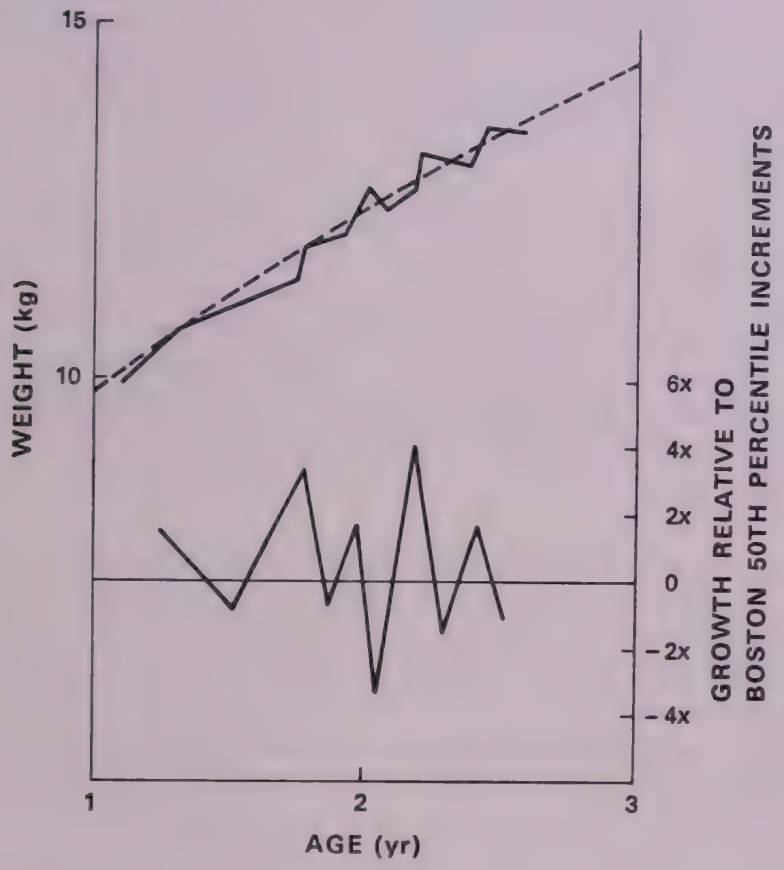
The amount of energy and protein that a child requires for health depends partly on the rate at which he is growing. Because linear growth is a relatively slow process in relation to growth in weight, and no estimates are available for its nutritional cost (although it must be minimal), it has become customary to base nutrient needs for growth on the rates at which weight increments occur at different ages, obtained by calculation from the Boston 50th percentile weight tables (Ref. 82). The daily nitrogen increments used in the FAO/WHO report were calculated from body composition data from year to year of age (Ref. 1). However, the additional allowance of 30 per cent over the safe level was assumed to cover any variation in annual individual rates of weight and height increments.

Healthy Children

In setting their safe allowances for dietary protein and energy for children, all national and international expert committees have assumed that rates of growth within a given age range are constant. Daily weight gains for children 13 months old up to age 17 years were calculated on the basis of the yearly increments divided by 365.

Although standard growth charts are presented as statistically smoothed curves, it is the common experience of everyone who measures child growth at frequent intervals that weight and height gains are by no means constant. This is immediately apparent from clinic growth charts (Fig. 4.1), but even these growth records are over-simplifications. Mothers usually visit well-baby clinics only at monthly intervals, which means that any observed growth variations are only an average for that period. Even for school children it would be methodologically difficult to obtain a truly accurate measure of day-to-day

FIG. 4.1. Periodic variations in the growth rate of a healthy child basically following the Boston 50th percentile



(Supplied by Dr. R.G. Whitehead)

growth variability because measurement error would make up a substantial portion of apparent weight differences. However, it is not unreasonable to suppose that if daily increments *could* be measured, a much greater variation from that observed in monthly data would be found. In fact, the rate of growth of children is influenced by a whole range of environmental factors, including food intake, disease, the degree of physical activity, social stimulation, emotional state, and endocrine balance. Thus, it is logical to conclude that even in healthy children, daily body mass gain is a variable that must be considered in arriving at appropriate dietary protein and energy recommendations. These arguments also apply to requirements for other essential nutrients.

Children Recovering from a Period of Growth Faltering or Weight Loss

The growth patterns during and after illness are, of course, even more complex. The pathophysiological events at the time of an infectious illness have already been discussed in Chapter III. The main consideration in the present section is the catch-up in body mass that should follow once recovery has been initiated.

Under ideal conditions, if the infection has been acute and height has not been stunted, a catch-up in weight gain will progress until the child regains his own normal weight for age. If the infection has been of a more chronic nature, or if the child has been subjected to repeated infections and height growth has been affected, the extent of this rapid catch-up in weight will probably be limited by the reduced height of the child. In either case, however, the child's nutritional needs will be raised for some time because of increased net tissue gain.

Periods of catch-up in weight must be looked upon as natural biological events. Even in the most hygienic surroundings illnesses occur, and these episodes are followed by accelerated rates of weight gain. The less ideal the environment, the more frequent and urgent is the need for such catch-up growth. While every effort must be made to improve environmental hygiene and reduce the frequency and range of infections, it is inconceivable that such measures will ever be 100 per cent successful. Thus, nutrition scientists have the responsibility for ensuring that recommendations for energy and all other nutrients in the customary diets of children are sufficient, not only for 50th percentile rates of growth, but for catch-up in weight as well.

It is pertinent here to consider the nutritional significance and the physiological meaning of weight deficits in the small child. Taking as an example a healthy 1-year-old child of normal body composition (Ref. 83) weighing 10.5 kg, it can be estimated that 6.2 kg of his weight are water, 2.5 kg are lipid, 1.5 kg are protein, with 0.3 kg other body components, including minerals. Relevant tissues in considering weight loss or deficit are adipose tissue and muscle. This reference infant would have approximately 3.5 kg of adipose tissue and 2.2 kg of skeletal muscle, with the fat and protein content of each of these tissues assumed to be 60 per cent and 20 per cent, respectively. Therefore, the fat content of adipose tissue is 2.1 kg and the protein content of skeletal muscle is 0.4 kg. As shown by the calculations in Table 4.1, weight deficit at this age therefore reflects mostly a deficit in adiposity, because even a 20–25 per cent muscle protein loss, which amounts to about 40 per cent of the maximum muscle wasting seen in severely malnourished children,

TABLE 4.1. Calculation of contribution made by adipose tissue and skeletal muscle to the weight deficit of a moderately malnourished child at age 12 months

HEALTHY CHILD	MODERATELY MALNOURISHED CHILD
Age 12 months Weight 10.5 kg Height 75.5 cm	Age 12 months Weight 7.0 kg Height 68 cm Weight for height = 87% Expected weight = 8.0 kg (100% weight for height) Weight deficit = 1.0 kg Creatinine height index = 0.85
Body fat and adipose tissue 23.9% body fat Total body fat = 2.51 kg = 0.42 kg structural + 2.09 kg adipose tissue fat Assume adipose tissue contains 60% lipid Adipose tissue weight = 2.09/0.6 = 3.48 kg = 33.1% of body weight	*Muscle mass* Expected = 1.68 kg Actual = 1.43 kg Weight deficit from muscle = 0.25 kg *Adipose tissue* Expected weight = 2.65 kg Deficit in adipose tissue weight = 0.75 kg
Body protein and muscle mass 14.6% body protein Total body protein = 1.53 kg Daily creatinine excretion = 110 mg Assume 20 g muscle = 1 mg creatinine Muscle mass = 20 × 100 = 2.20 kg = 21% of body weight Muscle protein content. assuming 20% protein, = 0.44 kg	*Protein and fat deficits* Protein deficit = 0.25 × 20/100 = 0.05 kg Protein deficit (% of weight loss) = 4.28% Fat deficit = 0.75 × 60/100 = 0.45 kg Fat deficit (% of weight loss) = 23.5% *Deficits in relation to normal child* For muscle and muscle protein = 35% For adiposity = 55%
Body water 59.0% body water Total body water = 6.20 kg	

(Based on Fomon, Ref. 83)

translates to 0.44 to 0.55 kg of body weight loss, while the percentage deficit for fat loss in adipose tissue amounts to 1.4 kg of body weight deficit.

Catch-up in Weight

In children who are underweight for their height, catch-up in weight can vary over wide limits, but maximum rates can reach very high levels indeed. During recovery in hospitals or rehabilitation centres from severe malnutrition,

rates of weight increments of up to twenty times normal for age have been reported (e.g. Ref. 84). However, it must be recognized that such high rates of weight gain have been achieved only during short periods of time by means of the regular, supervised feeding of special energy-dense formulas, and it is difficult to suppose that such rates could be achieved in the community at large.

The magnitude of catch-up in weight that can be obtained in more natural circumstances has been demonstrated in recent prospective longitudinal studies such as those carried out by members of the working group in Lawrence Tavern in Jamaica, Namulonge in Uganda, and Keneba in the Gambia. These are all in rural areas served by well-run child welfare clinics, and thus accurate anthropometric data are available.

Table 4.2 shows monthly incremental changes in weight for the three communities in children ranging in age from 10 months to 2 $\frac{1}{2}$ years. Because the distribution of weight changes is not normal, variations in rates of weight change are recorded in percentile form. For reference purposes, growth velocities based on the Boston 50th percentile weights are also recorded. From Table 4.2 it can be concluded that rates of weight gain up to four or five times the Boston 50th percentile growth rate occur with high frequency in all three communities, and thus such growth velocities are a realistic measurement of what must be taken into account in such rural communities. Similarly, Table 4.3 shows remarkably high rates of weight gain in Jamaican children whose growth had previously been inhibited by undernutrition and infectious disease.

Nutrient Requirements for Catch-up Growth and Tissue Repletion

A primary requirement is that the child must receive sufficient dietary energy and nutrients to enable him to achieve his growth potential. Growth rate will vary from day to day according to his physiological and health status. In circumstances where there is a considerable weight deficit, requirements will normally be high in order to reduce or abolish this deficit. Weight deficit can be made up either quickly by a relatively large daily increase in food intake, or more slowly by a smaller increase. In an ideal environment there might be little benefit from trying to achieve too rapid a rate of catch-up growth. However, in most situations in the developing world, a child is subjected to repeated episodes of acute infection, and if catch-up growth between infections is slow, a cumulative defict builds up. It is of great practical importance that more information be obtained on the optimum dietary conditions for the correction of such growth deficits.

TABLE 4.2. Variations in monthly growth increments in pre-school children in three different communities

Age (months)	No.	Percentiles of weight change		
		3rd	50th	97th
Uganda				
10–12	92	—724	217	977
13–15	99	—579	174	869
16–18	83	—805	145	1086
19–24	179	—521	174	869
25–30	126	—553	217	869
Gambia				
10–12	193	—819	95	760
13–15	159	—652	108	760
16–18	144	—819	117	984
19–24	346	—869	109	936
25–30	241	—811	117	1014
Jamaica				
10–12	616	—189	227	642
13–15	401	—189	189	605
16–18	579	—340	189	680
19–24	700	—302	151	718
25–30	700	—378	151	718

Increments at the Boston 50th percentile used by WHO/FAO (1973) were:9–11 months, 330g month; 1–2 years, 208 g/month; 2–3 years, 170 g/month.

The Basic Problem

One fundamental practical problem encountered in most rural communities is that traditional foods are often of relatively low-energy density, and this in itself, quite apart from nutrient content, seriously limits the child's ability to put on weight quickly. When this problem has been overcome it is essential to ensure that the concentration of protein relative to energy content is also adequate. Concern is not only for energy and protein, but for all essential nutrients so that these, in turn, do not become limiting factors to growth. For example, even with a milk-based infant food closely resembling human milk, the addition of zinc under some circumstances can result in significant increases in height and weight (Ref. 85).

During recent years, various attempts have been made to estimate how much energy and protein are required by children who need to restore body tissue lost as a consequence of poor nutrition and infections. In determining

TABLE 4.3. Percent of normal weight gain of Jamaican children under 5 years of age for each of the three monthly increments after faltering

% of normal	Boys		Girls	
	No.	%	No.	%
< normal	157	(33.6)	164	(39.2)
100–199	182	(39.0)	142	(34.0)
200–299	82	(18.2)	88	(21.0)
300–399	26	(5.6)	14	(3.4)
400–499	12	(2.6)	6	(1.4)
> 500	7	(1.5)	4	(1.0)
Total	466		418	

requirements for catch-up in weight, one should, in theory, consider the composition of the tissue lost and therefore in need of being repleted. Any variations in this will influence the quantities of nutrients required to make up the deficit.

The metabolic consequences of acute infections and of starvation differ with host characteristics and the type of infection. It has been pointed out in Chapter III that during certain infections in well-nourished volunteers there can be a disproportionately greater loss of muscle protein than of body fat, whereas in starvation the converse may occur, depending in part on the initial size of the fat store and duration of the fast. In the undernourished child experiencing repeated infections and anorexia, both factors are operative and the overall metabolic responses are more complex and difficult to predict.

More information is required to define the type of tissue lost under various circumstances and, consequently, what the nutritional requirements are for repletion of body mass. The examples given at the end of this section clarify these concerns.

Calculated Protein Requirements for Catch-up in Weight

A 1-year-old child weighing 7 kg and having 87 per cent of ideal weight-for-height (50th percentile for height and age, Boston standards) is very common in rural and urban poor populations in developing countries. Height is near 68 cm (91 per cent of the 50th Boston percentile, or below the 3rd percentile of the same standards). Therefore, the child is both stunted and under-weight at this age. The weight deficit for height is 1 kg, and 3.5 kg for age. This

child has second-degree malnutrition according to the Gomez classification (Ref. 86). However, in estimating optimal weight gain, 1 kg should be the immediate aim, even though the child may still be 24 per cent below normal for age.

Protein requirements for growing children have been based on estimates for maintenance plus those for average daily net body protein gain. Two different situations must be considered in calculating requirements for catch-up in weight: (a) severely malnourished children during recovery, and (b) mildly to moderately malnourished children commonly seen in "poor" populations.

1. Severely malnourished children

Severely malnourished children have lost both adipose tissue and protein, primarily from muscle. The marasmic child who is essentially devoid of adipose tissue has a severe body-weight deficit, but this child may still have up to 85 per cent of his expected muscle mass for height. However, if the duration of the marasmic state is prolonged, or if an infection occurs, the child may become rapidly protein-deficient, losing up to 55–60 per cent of muscle mass. At the other extreme, a severely malnourished child with kwashiorkor may be fat, but the muscle mass may be severely reduced. Weight deficit in this situation is small. Generally, however, the severely malnourished child (marasmic kwashiorkor) has similar percent deficits in adiposity and in muscle mass, and therefore the assumption that he or she must put on weight of normal composition (similar to that in normal growth) is a valid one.

An early attempt (Ref. 87) to calculate the requirements to cover catch-up growth in severely malnourished 1- to 2-year-old children weighing 7 kg is shown in Table 4.4. The data were based on the incremental method of estimating protein requirements employed by the British Department of Health and Social Security (DHSS). It will be seen that if feeding a protein with an NPU of 0.75, an intake of 1.59 g/kg/day theoretically would be adequate for an *average* rate of growth of 10 g/day, but to grow at 70 g/day the average child would require a level of protein up to 3.26 g/kg/day.

Waterlow and Payne (Ref. 88) have carried out similar calculations, and their values are given in Table 4.5. Here the basis was a normal 1-year-old child, and with egg or milk protein it was calculated that protein intake would need to be raised from 1.25 to 1.85 g/kg/day to achieve an increase in growth of five times the normal rate for a child of this size. The proportionate increase in protein requirements would not have been so great had a larger starting body weight been selected for these two series of calculations.

TABLE 4.4. Protein, energy, and P/E ratios for catch-up growth in an average child weighing 7 kg recovering from severe malnutrition

Rate of growth (g/d)	Protein (g/kg/d)	Energy (kJ/kg/d)	P/E ratio (%)
10	1.59	472	5.6
30	2.13	514	6.9
50	2.69	555	8.1
70	3.26	598	9.1

The data are based on those of Whitehead (Ref.87). It was assumed that the diet has an NPU of 0.75. No allowance has been made for variations in individual efficiency for protein utilization.

TABLE 4.5. Protein and energy requirements for catch-up growth in a one-year-old child

Growth rate		Protein (g/kg/d)	Energy (kJ/kg/d)	P/E ratio (%)
Maintenance + normal growth	× 1	1.25	465	4.55
	× 2	1.40	490	4.80
	× 3	1.55	515	5.05
	× 4	1.70	540	5.30
	× 5	1.85	565	5.50

Data, from Waterlow and Payne (Ref.88), based on requirements for milk or egg protein. Protein increment for normal growth was taken as 0.15g/kg/day.

2. Mildly to moderately malnourished children

These children often have a body-weight deficit of about 13 per cent for their height, and their muscle mass is close to 85 per cent of that expected for their height. Weight-for-age deficit would be 33 per cent (Gomez second-degree malnutriiton). Weight loss due to muscle-wasting amounts to about 31 per cent, while that due to adipose-tissue deficit is 9.4 per cent of that expected for height. In terms of weight-for-age, these deficits are much greater.

Whitehead (Ref. 87), in his original calculations, chose 7 kg because it was the typical weight for 1- to 3-year-old children requiring treatment for kwashiorkor in Uganda, (although marasmic children were smaller). Subsequent experience in the Gambia, however, has demonstrated (Ref. 89) that many children living under prevailing rural conditions remain around this weight during the 1- to 3-year-old period; even the average child's weight is only 7.4 kg at 1 year, 8.3 kg at 18 months, and 8.9 kg at 2 years.

Similarly, in South India Rao and co-workers (Ref. 90) have reported that in underprivileged children the average weight of a 20-month- to 2-year-old boy is only 8.7 kg, and of a girl, 7.8 kg. Clearly, calculated protein requirements for children in the critical 1- to 3-year-old period, based on 7 kg, are of practical relevance to customary home life in various parts of Africa and Asia, but it is equally obvious that any future research directed at determing protein requirements for catch-up would need to pay due attention to the initial weights of children encountered in a wider range of public health situations.

Theoretical Energy Requirements for Catch-up

It cannot be stressed too much that growth is as much dependent on adequate supplies of dietary energy as on protein and the other essential nutrients. Calculations for energy requirements are complex, depending on the origin of the weight deficit (mostly nutritional, or mostly as a consequence of an acute infection), its severity and duration, age and activity of the child, etc.

In the rehabilitation of malnourished children, an attempt should be made to keep children active, as this is important to overall recovery. For this purpose, Whitehead (see Table 4.4) made an allowance of 175 kcal (732 kJ) per child, but obviously this was only an assumed value and emphasizes the need for more experimentally determined measurements of energy expenditure in children during rehabilitation under home conditions.

Another problem in estimating energy requirements for weight gain concerns the value used in the calculation to support different degrees of weight gain. For the older data in Table 4.4, a value of 24 kcal (100 kJ)/g *protein deposited* along with other cellular constituents was used, while in Table 4.5, 6 kcal (25 kJ) per g *total weight gain* was employed.

These are some of the reasons for the differences between Tables 4.4 and 4.5, but both show that, while energy requirements do increase for more rapid rates of growth (g/kg) in the severely malnourished child, this is not as great as the calculated increase in need for protein, and consequently the protein/energy ratio (P/E) apparently should be increased if catch-up growth with a "normal" composition is to be achieved.

The values in Table 4.4 assumed an NPU of 0.75; the P/E ratio for a growth rate of 10 g/day was 5.6, while for 70 g/day it was 9.1. It is difficult to relate these growth rates to those of normal children; 7 kg would, under more ideal conditions, be the weight of a child around 5 months of age with an average growth velocity of 19 g/day. The rate of growth of a 1- to 2-year-old child would normally be about 7 g/day.

The values in Table 4.5, which are based on more recent information, indicate that P/E ratios need not be increased by quite so much, and it is important that this subject receive greater research attention.

Moderately malnourished children pose a different question, because weight loss is due mostly to a loss in adiposity. Protein depletion and repletion in these children cannot be properly assessed by changes in weight for the reasons previously stated. Table 4.6 presents the theoretical calculations of energy and protein requirements for a child weighing 7 kg, whose weight-for-height deficit is 1 kg, and who is to recover the weight loss in 60 days. In one case, the child has had a severe infection. In the other, the child has had progressive, chronic PEM without a recent severe infection.

Another possibility not taken into account is that a body-weight deficit leads to a greater efficiency of nitrogen utilization, and this, too, should be investigated. Also needed are criteria that will help to distinguish between true catch-up growth, which includes greater velocity in linear growth and is, therefore, a long-range goal, and the repletion of tissue losses for a given height.

Rehabilitation in Hospitals and Health Centres

In the hospital setting, it is relatively easy to achieve very rapid rates of growth by feeding a modified milk formula; that is, one in which the protein is maintained and the energy density is increased. The composition of these milk-based diets and the amount and frequency of feeds needed to produce rapid catch-up growth have been described in detail (Refs. 91–93). The question is often asked as to whether growth rates of ten to twenty times the normal rate are harmful. To our knowledge, no ill effects have been demonstrated, provided high-energy feeds are not instituted too early and that adequate minerals and vitamins are supplied. For the hospitalized child there are economic and psychological advantages associated with a rapid recovery. Although measurements of nitrogen balance and lean body mass suggest that there is a rapid deposition of new protein, it is not known to what extent the process advances harmoniously in all tissues. This is a problem for future research.

Manifest practical problems are encountered when one wishes to allow for catch-up growth at home. Under village conditions, rates of weight gain comparable to those achieved in the hospital are unlikely to be obtained unless the dietary pattern is changed to an impracticable extent. Even modest rates of catch-up growth are unlikely to be attained under village conditions unless the traditional diet is substantially modified and meal frequency

TABLE 4.6. Theoretical considerations of protein and energy needs to allow catch-up in weight of a one-year-old moderately malnourished child without and with a previous infectious episode

A.	Child's height = 68 cm (50th percentile of a 5-month-old child). Weight-for-age = 67%; weight-for-height = 87%. Creatinine height index (CHI, Ref. 106) 0.85. Infectious episode has produced an added 300 g weight loss and 14% muscle protein loss (CHI 0.71).	
B.	Components of weight *deficit:*	
	Without previous infection	Following infectious episode of 7 days duration
	Adipose tissue mass: 750 g (9.4% of body weight-for-height)	Adipose tissue mass: 750 g (9.4% of body weight-for-height)
	Muscle mass: 250 g (3.1% of body weight-for-height)	Muscle mass: 550 g (6.8% of body weight-for-height)
C.	Protein and energy needs above recommended intakes for a 5–month-old child (height-age of the child) for repletion of the deficits in body components	
	C.1 Repletion in 60 days	
	Protein: 83 g = 0.2 g/kg/day	Protein: 160 g = 0.38 g/kg/day
	Energy: 5800 kcal for adipose tissue repletion + 620 kcal for protein repletion.	Energy: 5800 kcal for adipose tissue repletion + 720 kcal for protein repletion.
	Total: 6420 kcal = 15.3 kcal/kg/day	Total: 6250 kcal = 15.5 kcal/kg/day
	C.2 Repletion in 30 days	
	Protein: 83 g = 0.4 g/kg/day	Protein: 160 g = 0.76 g/kg/day
	Energy: 6420 kcal = 30.6 kcal/kg/day	Energy: 6520 kcal = 31 kcal/kg/day
D.	Protein and energy needs per kilo per day for child: Recommended for normal 5–month-old child: 1.8 g protein and 105 kcal/kg/day. P/E ratio = 6.8%	
	D.1 Repletion in 60 days	
	2 g protein/kg/day	2.2 g protein/kg/day
	P/E ratio 6.7%	P/E ratio 7.3%
	120 kcal/kg/day	120 kcal/kg/day
	D.2 Repletion in 30 days	
	2.2 g protein/kg/day	2.56 g protein/kg/day
	P/E ratio 6.5%	P/E ratio 7.5%
	135 kcal/kg/day	136 kcal/kg/day
E.	Assumptions: energy absorption 90%; protein retention 60% (mean for recovering children)	
	Energy needs to synthesize: 1 g protein = 7.5 kcal	
	1 g fat = 11.6 kcal	

increased. The efficacy of such modifications, however, would have to be proved by carefully designed operational research; one cannot simply extrapolate from metabolic ward experiences. To be successful, any modification would have to take into account not only food preferences and availability, but also cost and time required by the mother to prepare them.

Bulkiness and low fat content of the traditional diet are frequently major limiting factors in providing the nutrients and energy required. Even with as many as five meals daily, fed *ad lib,* Ugandan children receiving their traditional home diet had significantly lower energy and protein intakes and slower weight gains than did children receiving a milk-based diet (Ref. 94).

The problem of energy density is well illustrated by examples from the Gambia and Jamaica. In the Gambia, infants are weaned onto gruels such as *sanyo mono,* which is made from millet. The protein/energy ratio of *sanyo mono* is 9 per cent and thus, from a theoretical point of view, it could be considered nutritionally adequate in protein content to support normal rates of growth. In practice, however, *sanyo mono* is prepared as a *thin* gruel so that 2.5 liters would have to be consumed daily to satisfy the energy needs of a 1-year-old child.

In Jamaica, a similar situation exists. Infants are commonly weaned onto corn-meal porridge, which is fed from a bottle. Consequently, the porridge has to be exceedingly dilute to pass through the nipple. Milk and sugar are added to the porridge, and it could be nutritionally adequate, but, because of the low energy and protein density, it would be necessary to give three 8-ounce bottles at each feeding. Such huge volumes are clearly impossible even for healthy children.

These practical problems should not be underestimated; applied and operational research on better ways of formulating practical diets based on the theoretical considerations detailed in this document needs to be encouraged. It is not sufficient merely to design a recipe; the effectiveness of any new food formula should always be tested under natural environmental circumstances. If a food is intended to promote catch-up growth, its ability to do so should be proved experimentally.

Complications Encountered in Subjects during an Actual Illness

As described earlier, even mild or subclinical infectious diseases cause a period of negative nitrogen balance and a loss of body nitrogen that must be made up later or the individual will be depleted. The effect is more pronounced if the gastrointestinal tract is involved. Similarly, energy balance is usually negative, and becomes more so with the degree of fever. As discussed in detail in Section III, the mechanisms responsible are multiple, but anorexia resulting in decreased food intake is a major factor, and in children the tendency to withdraw solid food is particularly important in further decreasing intake.

For protein status, other major factors are the stress response, culminating in mobilization of amino acids from skeletal muscle and their deamination in the liver for gluconeogenesis and the synthesis of so-called acute-phase proteins as part of the immune response. Energy balance is affected mainly by the reduced food intake, but frequently also by the increased basal metabolic rate associated with infection.

The net effect of these changes is to increase the needs for dietary protein and energy if significant depletion is to be prevented, particularly if the infection is prolonged, or if acute infections are repeated at frequent intervals, as is the case in the populations of developing countries. The current literature indicates that the stress resulting from infection may have differential effects on the metabolism and utilization of individual amino acids, and that not all infections have the same qualitative and quantitative effects on body protein and amino-acid metabolism. This makes it difficult to predict the quantitative significance of the effects of infection on dietary needs for energy and protein.

Moreover, although the metabolic effects of many kinds of infections on the intake, metabolism, and excretion of nutrients have been studied in considerable detail in well-nourished subjects, there is a serious lack of comparable data about the malnourished host. There is also almost no quantitative information on differences in the efficiency of utilization of dietary energy, protein, and essential amino acids in healthy and depleted subjects during and immediately after infection. There is, therefore, uncertainty as to how protein and energy requirements are affected for individuals in population groups where there is a high incidence of both malnutrition and infections of different kinds.

There are many data in the older literature, some from the past century, citing the cumulative negative nitrogen balance associated with a wide variety of acute infectious illnesses, ranging from otitis media and the common communicable diseases of childhood, to such severe illnesses as meningitis and pneumonia (Ref. 75). Powanda (Ref. 95) summarized data from a number of such reports of patients with acute infectious diseases. Adding the total nitrogen losses and dividing them by the days of illness of all subjects, an average daily negative nitrogen balance of 0.6 g of protein/kg was obtained (Ref. 53). Tabulating separately those infectious illnesses associated with diarrhoea or dysentery brought the average loss to 0.9 g protein/kg/day. Some of the highest losses, namely 1.2 g of protein/kg/day, resulted from the effects of typhoid fever, but the losses attendant on other infections, especially those associated with prolonged diarrhoea or dysentery, were sometimes as great.

Clearly, such losses must be made up during the recovery period, and the diet

must contain sufficient protein relative to its energy density for this to occur as expeditiously as possible. The time required for recovery and return to nitrogen balance is often far longer than the apparent duration of the acute episode. One day of diarrhoea or fever may result in up to a week of increased efficiency of dietary nitrogen utilization and retention with an adequate diet.

Estimation of the quantitative need for protein and energy during recovery from acute infections depends on how much longer should be allowed for recovery than the duration of the acute episode and what baseline is taken for the needs of healthy individuals of the same age. Based on an allowance of four times as long for the anabolic phase of recovery, it may be calculated that each day of the catabolic phase of an acute, severe infection would require from 0.15 to 0.30 grams of protein per kg (Ref. 53). If one takes the intermediate value of 0.9 g of protein/kg/day additional body protein loss, as seen, for example, in a child with scarlet fever, approximately 0.2 g/kg/day of egg or milk protein would be required during the recovery period, and correspondingly more protein from dietary sources of lesser quality.

Corresponding data on the energy requirements caused by acute infections are simply not available, but increased energy needs may be substantial, especially when the increased metabolic rate and related increase in protein turnover associated with fever is added to the effects of reduced food intake. Reduced activity probably compensates, at least partially, during both the acute episode and the early phases of recovery. However, it is not possible to calculate a P/E ratio for recovery from infection without relying upon some highly arbitrary assumptions. For recovery from most infections, P/E ratios in the range of those proposed to allow for catch-up growth of severely malnourished children should be adequate.

For chronic infections that interfere with gastrointestinal absorption, the issues are equally difficult to resolve, because carbohydrate, fat, and protein absorption may all be affected, and the magnitude of the effect varies so much with environmental and host factors. There is an urgent need for more quantitative data on the effects of chronic enteric infections on nutrient and energy requirements.

V. RESEARCH CONSIDERATIONS

The Overall Problem

1. Energy

It is not always recognized that the lower energy intake of many less-privileged populations may be a handicap to their potential for economic productivity and social development, and is part of a vicious circle that needs to be broken by wise guidance of the development process. Moreover, from the standpoint of goals for agricultural production, this means that more food needs to be produced, and also that a way to generate the purchasing power necessary to obtain adequate food should be part of development plans (e.g., Ref. 96). In order to identify optimum targets for food production relative to considerations of health maintenance, knowledge of the energy requirements of groups of individuals of all ages under varying environmental and cultural circumstances must be increased substantially.

Attention should be given to each age group: infants, pre-schoolers, primary-school children, adolescents, and adults of all ages. In the case of the elderly in industrialized countries, reduced physical activity and lower basal metabolic rate imply lower energy needs, but the total protein need may not decline proportionately (Ref. 97). Thus, higher protein/energy ratios than those for young adults may characterize the relationship between protein and energy requirements during the later years of life. Particular emphasis must now be given to individuals in the developing regions where work and activity patterns differ substantially from those of the subjects upon whom much of the current data are based.

At present, estimates of the energy requirements of human subjects are based largely on dietary survey data and on a limited amount of information about patterns of physical activity and the energy cost of various physical activities.

Apart from the difficulties involved in determining nutrient intakes precisely, it is not certain that the current recommendations are optimum for long-term maintenance of normal body composition and function. This matter can only be resolved, however, through additional research on the dietary energy requirements of humans and on the quantitative significance of factors that affect them. Thus, for the populations of concern in this report, there is little or no information on the energy cost of activities and energy usually expended by children, non-pregnant, pregnant, and nursing women and other adults. The impact of undernutrition, acute and chronic infection, and of catch-up growth on these aspects of energy requirement and utilization must also be defined.

In part, this will require advances in methodology for measuring energy intake and expenditure in individuals engaged in their usual daily activities and in population groups. It also requires better understanding of the reciprocal relationships between the adequacy of dietary energy and physical activity. Because there is no single level of energy requirement independent of the activity pattern of the individual, this too must be defined in terms of the range compatible with desirable social functioning and health status. When does reduced activity as an adaptation to lower dietary energy availability become socially, economically, or medically unacceptable? What range of activity is most compatible with the maintenance of good health? What methodology can be developed to obtain answers to these questions?

Clearly, caloric intakes in excess of needs imposed by the level of physical activity will lead to over-nutrition and obesity. This is equally as undesirable as insufficient energy intakes, because of the adverse health consequences of excessive energy intake: namely, increased frequency of hypertension, heart disease, diabetes, and perhaps greater susceptibility to infection (Ref. 98) and decreased work performance (Ref. 99). It is also a gross waste of a nation's resources. Indeed, the frequency of obesity as a public-health problem in the industrialized societies, where most of the dietary data have been gathered, suggests that current recommendations may not be appropriate.

2. Protein

Although many studies have been carried out on the protein requirements of humans, these are mostly short-term and largely limited to well-nourished Caucasians. Hence, knowledge of human protein and amino-acid needs is still extremely limited, especially for individuals in developing countries. It is crucial to obtain information on the protein requirements of children, pre-school and school-age, non-pregnant, pregnant, and nursing women, and of the adults of populations in developing countries considered in relation to local foods and diets, environmental conditions, and patterns of living.

Data on the requirements for individual essential amino acids are highly inadequate and unavailable for various age groups. In this context, the protein nutritional value of diets typical for population groups in developing countries, and the impact of the age of the individual on the nutritional value of habitual diets, deserve particular attention. The significance of current estimates of protein and amino-acid needs for long-term health has not been established, although a series of recent papers has raised serious doubts about their suitability even for healthy, well-nourished adult subjects (Refs. 46, 100, 101).

Recent data substantiate the sensitivity of body nitrogen metabolism to the level and adequacy of energy intake (Refs. 59, 102, 103) and the difficulties created by this response for arriving at reliable estimates of dietary protein requirements. Furthermore, studies have also confirmed that an improved retention of nitrogen can be achieved by feeding protein of better quality even under conditions of dietary energy inadequacy (Ref. 104). Little is known, however, about the physiological significance of the additional nitrogen retained under these conditions, or the extra nitrogen retention brought about by excessive energy intakes (Ref. 105). This requires, in part, the development of functional indices of the protein and energy nutritional status of individuals.

The quantitative extent to which apparently low dietary energy intakes are of practical importance in altering dietary protein utilization and requirements must be determined. If the latter are compensated for by reduced activity, there may be no significant effect on protein metabolism and utilization. It is essential that metabolic balance studies concerned with nitrogen balance in humans at any age pay meticulous attention to recording and analyzing the effect of variations in energy intake or energy expenditure on nitrogen metabolism and dietary protein utilization.

3. Regional and Community Considerations

In addition to the above, the series of research recommendations of the 1975 FAO/WHO meeting (Ref. 58) are highly relevant and should be pursued as opportunity permits. These include (a) the need for data on the basal metabolic rate of various population groups; (b) data on the health consequences of physical inactivity; (c) the effect of climate on energy and protein requirements; (d) the degree of metabolic compensation for increased sweat losses; (e) the biologic significance of seasonal variations in food intake and body weight; and (f) the digestibility of protein and energy sources and the biological value of protein in local diets.

The latter is particularly important in view of the fact that various dietary, as

well as host and environmental factors, may modify the utilization of nitrogen and energy from diets when consumed under field conditions. Furthermore, there is an urgent need to assess the applicability of available data on the nutritive value of dietary constituents, as determined in well-nourished subjects under the conditions of well-defined metabolic balance studies, to dietaries and conditions that characterize populations in developing regions.

Priority Research Areas for the United Nations University World Hunger Programme

The above paragraphs emphasize the broad areas where specific knowledge of energy and protein requirements is lacking for populations in developing countries. A series of priority research areas can be identified, as follows.

1. Energy Requirements and Expenditure

There is an urgent need for more information on these subjects.

(a) The energy expenditure of pre-school and school-age children, and of men and women of differing physiological, nutritional, and health status must be studied. This, together with studies of the energy cost of various physical activities in these groups under normal living conditions, is basic to an evaluation of the energy requirements and nutritional status of the populations in developing regions.

(b) The influence of energy intake and of physical activity on the utilization and need for dietary protein should be investigated.

(c) There is a need for more information about the social and health significance for populations consuming dietary energy at levels substantially below those found approrpiate for healthy individuals in more privileged economic and social circumstances.

(d) The costs in human welfare and economic productivity of suboptimal calorie intakes should be determined and compared with the costs of correcting the situation. Particularly needed are convincing, practical demonstrations of the extent to which increased dietary energy results in productivity and other social gains in free-living conditions without artificial productivity incentives that could not be maintained on a continuing basis in the society.

2. Protein Requirements and Allowances

There is an urgent need to determine the following matters.

(a) Whether there are constitutional differences (genotypic) of practical importance in the protein requirements of different population groups is

a question of great importance. In consideration of present knowledge, university students in a developing country may provide an adequate basis for initial comparison with comparable groups studied elsewhere and in a similar manner.

(b) The current estimated safe practical intakes for protein must be evaluated for the diets and food sources typical for both adults and children in developing regions.

(c) The capacity of these diets to meet protein intakes necessary to maintain an adequate protein nutritional status under the prevailing environmental conditions must be determined. This involves an assessment of the chronic environmental factors in developing countries that influence the need for dietary protein (phenotypic factors), both in absolute terms and in relation to dietary energy intake and requirements. Studies of this kind should involve examination of those individuals exposed to the stresses resulting from an unsanitary tropical environment and consuming usual diets in which dietary fibre and other factors may alter protein availability. The importance of exploring the capacity of traditional diets to meet nutrient requirements is crucial.

(d) The effect of repeated episodes of infectious diseases on overall protein requirements for adequate maintenance and growth must be studied.

Limited resources and common-sense priorities indicate that such studies should concentrate on the most vulnerable groups: infants and pre-school children, pregnant and lactating women, with the pregnant adolescent representing an important and particularly vulnerable group. However, for various methodological and ethical reasons, and because there are more comparative data available for adults, it is also essential to continue studies among adults.

For studies concerned with protein needs and utilization, additional criteria of adequacy beyond nitrogen balance should be employed. These may include the measurement of body composition components, such as body cell mass by whole body ^{40}K measurement where possible; creatine and creatinine excretion as indicators of muscle-mass breakdown; serum proteins and amino-transferases (transaminases) as indicators of liver function; immune response, and tests of physical capacity or endurance. The status of visceral protein should be assessed by measurements of a variety of specific types of serum proteins. These include albumin, transferrin, haptoglobin, $alpha_1$-acid-glycoprotein, $alpha_2$-macroglobulin, $complement_3$, and immunoglobulins.

3. Requirements for Catch-up Growth and Effects of Infection on Nutrient Utilization

The estimates discussed in Chapter IV of the energy and protein needs and of

the P/E ratio necessary for recovery of weight loss and resumption of adequate growth following mild to moderate protein-energy malnutrition, with and without infection, are based on a number of assumptions. It is necessary that the latter be validated in order to develop sound and rational recommendations for the dietary energy intake and protein/energy ratio for populations within which there is widespread undernutrition and where chronic and acute infections are endemic.

(a) The protein and energy deficits associated with weight loss and reduced growth in children must be measured. In addition, the adequacy of catch-up weight gain as an indicator of catch-up growth should be explored. This will involve an assessment of body composition changes in children of differing ages and with varying forms of malnutrition during and following nutritional rehabilitation.

(b) The energy and protein/energy ratio of diets based on traditional foods that are adequate for ensuring rapid catch-up growth must be determined. Particular attention should be given to the influence of age and initial body size, because these factors need to be evaluated in the development of appropriate dietary guidelines. Initially, it is envisaged that these studies should be extended to the community in order to utilize critically the results obtained in the metabolic investigations for developing dietary guidelines and recommendations.

Concluding Comment

Although these research areas are concerned with protein and energy requirements, the adequacy of *all* essential nutrients must be of concern in both the design of research studies and any consequent community activity programmes. The role of these other nutrients for nutritional health in developing-country populations, and the contribution that the United Nations University could make to the acquisition of more complete knowledge of nutritional requirements in developing countries, should be considered by subsequent working groups and reports.

APPENDIX: STANDARDIZED CRITERIA FOR COMPARATIVE NITROGEN-BALANCE STUDIES OF PROTEIN REQUIREMENTS IN CHILDREN AND ADULTS IN DIFFERENT PARTS OF THE WORLD, CONSUMING DIETS BASED ON TRADITIONAL SOCIAL PRACTICES

Introduction

The data in previous sections on nutrient requirements and allowances for maintenance, recovery from stress, and growth for return to normal weight-for-height, are based on only limited observations from experiments, and much of the discussion is based on theoretical considerations that require verification by direct study. The practical and economic implications that arise from a number of issues raised in this report are immense, and they need to be investigated through careful research. The purpose of the studies outlined in this Appendix is to determine the amount of protein in habitual diets and in a diets based on a standard, high-quality reference protein required for nitrogen balance by individuals of different ages, ethnic backgrounds, in various physiological states, and under different environmental circumstances.*

The specific questions considered here are: First, are there any nutritional advantages to be derived from increasing the P/E ratio in the diets of adults and of growing children living under the conditions prevailing in developing countries? And second, if the answer to the first question is affirmative, what are the appropriate correction factors to be used in order to arrive at recommendations applicable to local diets, diets differing widely in the types of foods eaten in different regions of the world?

Methodology

The experimental approach proposed at this stage concentrates on the

* For reasons discussed earlier in the report, measurements of obligatory nitrogen are no longer considered directly useful as a basis for estimating nutritional requirements, and the more direct measure of nitrogen balance is preferable for this purpose.

amount of nitrogen, at physiologically appropriate levels of energy intake, necessary for nitrogen balance in adults and growing children. For children recovering from infectious disease, the amount of nitrogen needed to achieve adequate retention would be anticipated to correlate linearly with the rate of catch-up growth required. Although functional criteria of nutritional adequacy would be preferable to nitrogen-balance measurements, the former are not available and/or cannot be applied in relatively short-term metabolic studies.

Basically, two approaches can be used to obtain this information. First, the approach based on direct nitrogen-balance studies will be discussed, and second, the epidemiological approach.

1. Subjects

It will be most useful to study individuals who have been living under environmental conditions characteristic of low-income populations in developing countries, although for the specific study, subjects are best brought into institutional facilities permitting standardized metabolic measurements. In the initial phases of these studies, the subjects should be of normal weight-for-height, based on the available standards that are considered best suited to the conditions characteristic of the country. For studies that include individuals found to be heavily parasitized, or to be suffering from chronic infection, the relevant fact must be carefully noted, and, when possible, the study repeated some months after the subject has been treated and judged fully recovered. Because conditions will vary greatly with the population and individual studies, even the study of a few individuals in a category will be useful when combined with data from other studies. There is, for the present, no practical upper limit to the number of subjects that could be usefully studied.

There is also a need for a study, using the approach described below, of a group of at least twenty apparently normal, healthy male university students, each in one academic centre, located in Asia, Africa, and Latin America. This would enable a valuable comparison with the data already available on North American Caucasians in the same age range. Such subjects should be free from acute infection or overt metabolic or neoplastic disease, as determined by medical history, examination, and routine laboratory tests, including a chest X-ray.

In the case of growing children, they should be 2 to 5 years of age and have been free from acute infection or any acute illness for at least one month prior to study. Health status should be evaluated by clinical examination and appropriate laboratory studies. It may be desirable to study children with chronic parasitic and other diseases, but these must be fully described.

However, metabolic studies to determine protein requirement should not be carried out on malnourished children because of the abnormal retention associated with depletion as well as because of the importance of providing them with optimum treatment. When previously malnourished children are studied, they should have been on an adequate diet for at least one month following recovery, as judged by a weight-for-height ratio within 10 per cent of the norm, by a normal creatinine-height ratio (Ref. 106) as well as serum total proteins or albumin within a normal range.

Subjects, or their legal guardians in the case of children, need to be fully informed of the purpose and risks of the study and should sign written consent forms. The experimental protocol should be approved by the appropriate Institutional Review Committee, and employment of physician-advocates unrelated to the study is recommended in order to provide independent assurance that the children's best interests are safeguarded.

2. Diets

Diets should be standardized, based on foods habitually consumed, and given in a meal pattern that is as similar as possible to that to which the subjects are accustomed. Where a reference-protein diet (egg or milk protein) is included in the studies, use may be made of a liquid-formula diet that conveniently allows for constant, controlled intakes. Complete vitamin and mineral supplements should be added to ensure that no vitamins or minerals are limiting.*

Subjects should be randomly assigned to dietary levels. A modified Latin square design may be used for this purpose. An alternative method is to assign subjects to an ascending or descending sequence of dietary changes, if this appears desirable, or if it is not feasible to assign subjects randomly to the treatment variables.

Energy intake should be determined by an experienced dietitian according to a standardized dietary interview, evaluating retrospective dietary habits, physical activity, and weight pattern. In the case of children with poor nutritional backgrounds, dietary energy should be estimated from standards for their age. Customary water intake should be determined and maintained with minimal variation during the experiment.

* Unless the goal is to include in the study the effects of other possible deficiencies in the diet on protein utilization. In this case, diets must be characterized not only for their protein and energy and dietary-fibre content, but also for all known vitamins and minerals, including trace minerals.

3. Experimental Design and Measurements

Nitrogen balance should be measured at multiple protein intake levels, ranging for adults from an upper level near the range of expected nitrogen balance, downward to one suitable for the calculation of a standardized net protein utilization (NPU) estimate. In children, no more than two levels below nitrogen balance should be examined in short-term studies, and in long-term studies, all protein intakes should allow for nitrogen retention and growth. Nitrogen balances should be calculated with appropriate allowances for integumental and miscellaneous nitrogen losses. Digestibility, biological value (BV), and NPU can be calculated at each level of protein intake in a similar manner, with urinary and fecal nitrogen losses corrected for their respective obligatory losses. The latter can be approximated from published estimates (Ref. 1). When integumental and miscellaneous nitrogen losses are not directly measured, values of 5 mg and 10 mg N/kg/day are suggested for adults and children, respectively. A critical assessment of the nutritional value of the food-protein sources examined should be made by calculations of the slope of the nitrogen-balance response curve and intercept of this curve with the point of nitrogen equilibrium in comparison with those for the reference protein.

For *adults,* the difficulties of obtaining accurate estimates of fecal output, and in consideration of adaptation to reduced nitrogen intakes, make desirable, for each test protein level, one day on a nitrogen-free diet, five days for adaptation to the test level, and then five days for the urine collections. This period would then be followed by a break period of three or more days. Fecal collections are best pooled for the last eight days at each test protein level. It may be feasible to use average fecal nitrogen loss for all diet periods in calculating nitrogen balance and digestibility, but this would need to be evaluated from the data obtained. A minimum of four test protein levels should be included.

In measuring the nitrogen-balance response of *children,* each protein level should be fed for seven days, and estimated apparent nitrogen balance should be calculated on the basis of the last three days. The protein-free day should be omitted, and a three-day break period interposed between the randomized test diets. When a Latin square design is used, the children should receive, during these three days, the same diet that was given for the three days prior to the beginning of the study. A minimum of four levels of protein should be evaluated, maintaining energy intake constant, using isocaloric carbohydrate replacement of protein.

The suggested dietary protein/energy levels to be evaluated for children and adults are shown in Table App. 1. Departures from this experimental design

TABLE App. 1. Suggested protein/energy levels to be evaluated

A. Using a reference protein (egg, milk, or other high-quality protein)

Subjects	Daily energy intake (kcal/kg)	(kJ/kg)	Daily protein intake (g/kg)					
Children	100	(418)	0.75	1.0	1.25	1.50	1.75	2.0*
Adults	40	(167)	0.3	0.4	0.5	0.6	—	—
% P/E			3	4	5	6	7	8

B. Using local protein sources (predominantly mixed vegetables and proteins)

Subjects	Daily energy intake (kcal/kg)	(kJ/kg)	Daily protein intake (g/kg)					
Children	100	(418)	1.0	1.25	1.5	1.75	2.0	2.25*
Adults	40	(167)	0.4	0.5	0.6	0.7	—	—
% P/E			4	5	6	7	8	9

*The lower and/or higher levels may not be reached, but this will depend upon the characteristics of the children studied and diets under evaluation.

can be anticipated, but should be justified by the investigator in his proposal.

Complete, accurately timed, daily urine collections should be obtained for each subject, and aliquots analyzed for total nitrogen and creatinine. The latter serves both as a check on the completeness of collection and as an indicator of muscle mass and body composition. Nitrogen intake should be calculated by measuring the total nitrogen content of dietary aliquots taken at intervals during each dietary period.

The Kjeldahl procedure or automated or semi-automated phenol-hypochlorite methods should be used for nitrogen determination. Great care must be taken to homogenize the fecal pools and to obtain representative fecal and diet samples.

Urinary creatinine should be determined, and the alkaline picrate procedure is convenient (Ref. 107).

The energy content of the diet and of stools should be measured. This should be performed by bomb calorimetry when possible, but a first approximation can be made from measurements of dry weight and fat content of feces.

The study should be replicated in the same or comparable individuals using,

on an interim basis, either good quality fresh or dried milk or egg protein as the sole dietary protein source to provide a basis for comparison among the various populations and with previously published data obtained from subjects in industrialized areas. Possible lactose intolerance is not judged to be a contraindication to the use of milk for this purpose (Refs. 108, 109)

Body weights should be monitored daily, with a precision scale, under standard conditions (8:00 a.m., pre-prandial, post-voiding, with minimal or no clothing). It is desirable to assess possible changes in body composition, and this can be done indirectly by means of daily measurements of urinary creatinine excretion and anthropometric measurements at the onset and the end of each dietary period. These latter should include measuring the circumference of the arm at the midpoint between elbow and shoulder while the arm is hanging loosely; skin-fold thickness of the tricepital region with the same arm position and at the same point where circumference is measured; and skin-fold thickness immediately below the tip of the scapula. The right side should be used for young children and left-handed older children and adults, and the left side for right-handed older children and adults Some investigators also find it useful to measure the circumference of the lower part of the leg at its largest level with the subject standing.

Basal metabolic rate should be measured using either open- or closed-circuit techniques.

In order to characterize better the initial metabolic and health status of subjects, blood should be drawn from an antecubital vein at 8:00 a.m. on the first day of the study, following a 10-hour overnight fast, and analyzed for glucose, urea nitrogen, electrolytes, albumin, total protein, creatinine, uric acid, triglycerides, cholesterol, and serum amino transferases (SGOT, SGPT). A full hemogram and urinalysis should also be made.

4. Long-term Studies

Ultimately, any conclusions regarding protein and energy needs derived from short-term balance studies must be confirmed by long-term feeding of those amounts judged adequate. It is disturbing that the studies of Garza *et al.* (Ref. 46, 100, 101) indicate that intakes that are not associated with detectably significant biochemical or functional effects after 30 days may be associated with significant adverse effects after two to three months. It is simply not practical to project the long-term studies that would be required to include the many variations in age, sex, physiological state, and genetic and environmental factors. However, even a few well-done studies will help to determine how extrapolations can be made from short-term studies and to verify the appropriateness of these assumptions. Feeding of a determined

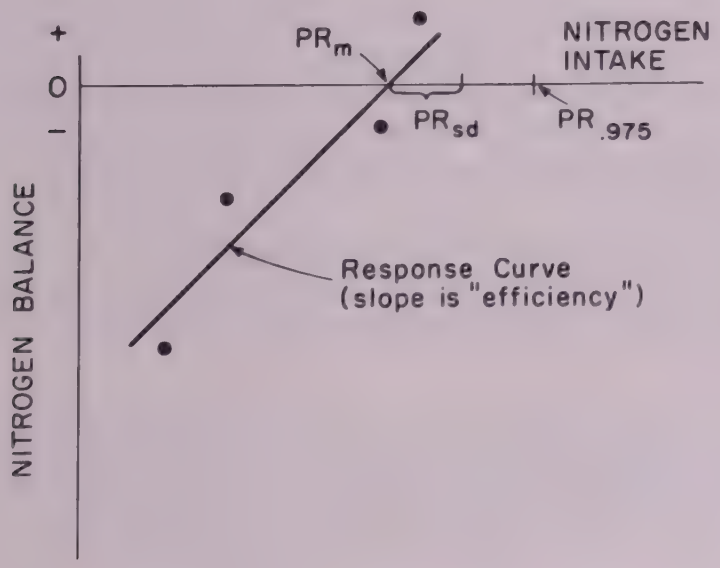
"safe level" for at least 60 to 90 days will be required, along with measurements of cumulative nitrogen balances, changes in body composition, a battery of biochemical measurements, and functional tests. When information is sufficient to expand such studies in adults to include children, the levels fed must ensure normal growth in height, weight, and body composition.

5. Analysis of Nitrogen-Balance Data

Linearity and significance of the nitrogen-balance response to increased nitrogen intake should be verified for each individual's response. Data for those subjects not meeting at least one of these criteria should be eliminated from the pooled data and reported separately, with every effort made to repeat the study with such subjects to determine whether the anomalous results were due to experimental error or some metabolic difference. A regression line, the mean, and 97.5 per cent confidence intervals for the zero-balance intercept should then be calculated, using the pooled data according to Method 3 described in the paper by Rand *et al.* (Ref. 60), as defined under "Mathematical Details."

This approach determines PR_m (intercept of nitrogen-intake with nitrogen-equilibrium line) from the regression line, estimating the variation in requirements directly, using the standard error of the estimate to define confidence bands for the response curve (Ref. 60). The intersection of the upper 97.5 per cent confidence band with the zero balance line provides the estimate of the protein allowance for the population (see Fig. App. 1.). The

FIG. App. 1.



advantage of this method is that both mean requirement and variability of protein needs are calculated directly from nitrogen-balance data obtained in the region of maintenance intake levels.

6. Overall Considerations in Nitrogen-Balance Studies.

(a) *Estimations of integumeutal and miscellaneous nitrogen losses.* The 1973 FAO/WHO report suggests 5 mg nitrogen per kg for combined integumental and miscellaneous losses, and this has been used as a basis for a uniform calculation for all ages. There is reason to believe that the true figure for children is somewhat higher because of their greater surface area (Ref. 110). An appropriate figure for infants and children can be obtained by calculating it in proportion to body surface area (BSA), given that a reference adult has a BSA of 1.73 m^2 and loses 300 mg nitrogen per day via integumental and miscellaneous routes. For adults, the 5 mg figure should continue to be used until more definite information is available.*

(b) *Dietary energy level.* It is of critical importance that the dietary energy intake approximate as closely as possible the usual energy intake of the individual. Some weight loss should occur during periods of negative nitrogen balance. The determination of dietary energy intake should be individualized. A starting point is to estimate the basal energy expenditure for a given body surface area and age. This is added to the extra energy needed for time spent on activities that have expenditures above basal. For children, an allowance should be made on the basis of the added requirements imposed by growth. For adults, a retrospective analysis of usual dietary energy intake by careful determination of the usual diet when body weight has been stable can provide a usuable estimate of energy required for balance.

Even small caloric excesses will increase nitrogen retention above normal levels, and deficits will have the opposite effect (Refs. 103, 112). *Estimates of normal protein needs from nitrogen balance are valid only when energy intakes closely approximate those when the individuel is consuming his usual* ad libitum *diet while maintaining his usual level of activity.*

(c) *Activity.* It is essential that activity be maintained as closely as possible to that usual for the individual when not under study, and as constant as possible from day to day during the experimental period. It is probable that

* The nitrogen retention unaccounted for by fecal and urinary losses in long-term balance studies with adults is approximately 15mg N/kg (Refs. 46, 111). This issue urgentiy needs resolution because it makes considerable difference in the amount of protein calculated as necessary for nitrogen balance. In the meantime, there appears to be no alternative to presenting both calculations for adults so that the effect of this uncertainty is clearly evident.

variations in energy need due to deficiencies in activity are important sources of daily variation in the balance results. It would be an advantage to assess daily energy expenditure of the subjects during the period of study. Techniques for this purpose vary, and the choice will depend, in part, upon the facilities available to the investigator. Minimally, a careful diary of activities should be kept.

(d) *Temperature*. An important source of variation in comparative studies will be the effects on integumental nitrogen losses of the temperatures to which the subjects are exposed during the study. The mean range of daily temperature and daily humidity at standard times should be recorded throughout the study. Where environmental conditions are such that sweat losses are likely to exceed significantly the normal insensible losses, an attempt should be made to estimate actual losses for representative subjects by collection and analysis of body sweat, such as that described by Calloway *et al.* (Ref. 113).

7. Co-ordination and Standardization

The responsible investigator for the United Nations University-sponsored studies should have had adequate training and experience in a UN University–associated reference laboratory or research project and/or benefit from the periodic visits of a UN University–designated co-ordinator for this programme.

The Dunn Nutritional Laboratory, Cambridge, UK, has been designated as the UN University reference laboratory for standardization of nitrogen determinations. The UN University will finance the exchange of samples. Dietary amino-acid composition must also be known, and if analytical resources are not locally available, arrangements can be made for the reference laboratory to undertake the measurement.

In addition to submitting a final report of the study, the responsible investigator will be expected to provide the original data on standardized forms to the World Hunger Programme office for central processing to aid in the further evaluation of the effects of population and environmental differences on the observed nitrogen-balance responses. However, the investigator will retain control of the primary data, and, after central processing, will be advised concerning the disposition of the combined data.

8. Pooled Response Method.

Given N data points of nitrogen intake (x) and nitrogen balance (y), of the form (x_{ij},y_{ij}) where i indicates individual and j represents level, the pooled response curve is calculated as:

$$y = a + bx, \text{ where}$$

$$b = \sum\sum (x_{ij} - \bar{x}\,..)\,(y_{ij} - \bar{y}\,..)/\sum\sum (x_{ij} - \bar{x}\,..)^2$$

$$a = \bar{y}\,.. - b\bar{x}\,..$$

$$S_e = \sqrt{\sum\sum [y_{ij} - (a + bx_{ij})]^2/(N-2)}$$

The protein requirement for $(1 - \alpha)\%$ of the population is:

$$PR_\alpha = \bar{x}\,.. + \frac{(-\bar{y}\,../b) + (t_\alpha s_{e/b})\sqrt{[(N+1]\,Q + (\bar{y}\,../b)^2/\sum\sum (x_{ij} - \bar{x}\,..)^2}}{Q}$$

where $Q = 1 - (t_\alpha s_{e/b})^2/\sum\sum (x_{ij} - \bar{x}\,..)^2$

$t_\alpha = (1 - \alpha)\%$ point on the Student t distribution

9. Longitudinal Studies

Valuable and relevant information on nutrient requirements for growth can be obtained from carefully analyzed growth data collected in parallel with information on dietary intake. Seasonal variations occur in food availability and nutrient intake, and these, in turn, lead to variations in growth rate. The prevalence of infection will also influence growth performance. Statistical analysis of data collected prospectively can be used to predict nutrient requirements under practical field conditions.

It is recommended that the UN University, together with WHO and FAO, draw the attention of the scientific community to the immense value of this type of work, which does not require sophisticated equipment or the availability of physical facilities that are necessary for conduct of precise metabolic balance studies. If possible, the UN University should provide support for well-designed studies of this type. Apart from the necessity for standardization of anthropometric measurements, particular attention must be focussed on the methods that are used to estimate food intake.

10. Additional Studies

Additional or more extensive studies of scientific interest can be incorporated into the protocol, provided that they contribute to the primary objectives. Examples of these are:

(a) whole body N turnover using amino acids labeled with stable isotopes;
(b) assessment of energy balance using direct or indirect methods for methods for measuring energy expenditure;
(c) biochemical measurements of plasma and urine for assessment of organ function: 3-N^τ-methylhistidine urinary excretion; serum amino

transferases; peptide-bound, non-dialyzable and total hydroxyproline excretion; energy substrates; and amino-acid profiles;

(d) measurements of digestive and absorptive functions of the gastrointestinal tract, such as D-xylose absorption, lactose tolerance, fecal-fat excretion, breath tests, and others;

(e) assessment of body compositional differences, indirect methods, such as densitometry, anthropometry, and ^{40}K; and

(f) other studies deemed pertinent by the investigators after discussion with, and approval from, the United Nations University.

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